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# MUMPS

## Use of Convalescent Serum in the Treatment and Prophylaxis of Orchitis

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MUMPS is a specific virus disease that is rarely serious in children but that produces a high percentage of severe manifestations in adults. In normal times, the study of patients admitted to contagious disease hospitals yields results probably not representative of the average disease, since these patients are usually a selected group with more severe types of mumps. The mobilization of large numbers of men in military service or an institutional outbreak provides an opportunity to make surveys and note the effects of specific therapy on this disease.

Mumps usually occurs between the ages of 5 and 15 years, the incidence being 10 to 20 per cent among persons who have spent their childhood in rural areas, while 80 per cent of those who have lived in urban districts had mumps in childhood. The high morbidity in the armed services is due, in the main, to the large number of susceptible persons from rural districts and to the intimate contact caused by necessary crowding. Under these conditions both the susceptible persons and those relatively immune have the disease during epidemics.

Johnson and Goodpasture [1] are generally credited with proving the existence of the specific virus in mumps. They showed that a filtrable virus exists in the saliva during the first forty-eight hours of the disease, that it is resistant to neutral glycerin, freezing and drying and that it is transmissible to rhesus monkeys through many generations and back to human beings. Granata [2] in 1908, Nicolle and Conseil [3] in 1913 and Martha Wollstein [4] in 1918 noted the evidence of a filtrable

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

1. Johnson, C. D., and Goodpasture, E. W.: An Investigation of the Etiology of Mumps, J. Exper. Med. **59**:1 (Jan.) 1934; Experimental Immunity to the Virus of Mumps in Monkeys, Am. J. Hyg. **23**:329 (March) 1936.

2. Granata, S.: Sulla etiologia degli orecchioni da virus filtrable, Med. ital. **6**:647, 1908.

3. Nicolle, C., and Conseil, E.: Essai de reproduction expérimentale des oreillons chez le singe, Compt. rend. Soc. de biol. **75**:217, 1913.

4. Wollstein, M.: An Experimental Study of Parotitis, J. A. M. A. **71**:639 (Aug. 24) 1918.

virus in this disease. Johnson and Goodpasture [1] in 1936 examined the parotid glands of rhesus monkeys to which they had transmitted the disease and described the pathologic changes during the acute stage. They found an edematous swelling of the salivary glands involved and the tissues surrounding, with pinpoint hemorrhages in the capsule. The glands showed parenchymal lesions and disintegration of the acinar cells and infiltration of mononuclear cells and lymphocytes.

It is probable that the virus enters the body by way of the mouth or nose. Gordon [5] stated that the most consistently entertained conception of mumps is that of a primary local disease of the parotid glands which arises from invasion of the buccal cavity, with progression of the virus along Stensen's duct and eventual production of a nonsuppurative swelling of the gland. Wesselhoeft [6] expressed the belief that it may reach the salivary glands by a roundabout course involving the blood stream. Philibert [7] originally proposed the theory that the virus finds its way first to the central nervous system by way of the conjunctiva and, being of a low neurotropic order, does not manifest itself clinically, but after an appropriate incubation period it enters the blood stream and produces its familiar symptomatology. This hypothesis would explain the fact that orchitis, encephalitis and pancreatitis can occur before, with or after an involvement of the salivary glands. He explained the involvement of the salivary glands on the theory that the virus is eliminated through them.

The most frequent complications are involvement of the gonads in men and of the pancreas, breasts, thyroid gland, thymus, lachrymal glands and Bartholin's gland.[6] Since it is probable that the virus enters the blood stream, the many so-called complications are more likely a part of the systemic manifestations of the disease proper.

Since the clinical signs of orchitis are so obvious, statistics concerning this condition are probably more accurate than those concerning other associated manifestations of this disease. Unless the observer was particularly interested in carefully noting all symptoms, many other statistics are of questionable value.

Orchitis occurs in an average of 18 per cent of men affected with mumps in epidemics,[6] although in individual groups the percentage reported has been as high as 66 per cent.[8] Wesselhoeft [6] stated that

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5. Gordon, J. E., and Heeren, R. H.: The Epidemiology of Mumps, Am. J. M. Sc. **200**:412 (Sept.) 1940.

6. Wesselhoeft, C.: Medical Progress: Mumps, New England J. Med. **226**: 530 (March 26) 1942.

7. Philibert, A.: Nouvelle conception de la pathogénie des oreillons, Progrés méd. **23**:145 (Jan. 23) 1932.

8. Bang, H. O., and Bang, J.: Involvement of the Central Nervous System in Mumps, Acta med. Scandinav. **113**:467 (April 17) 1943.

in different epidemics strains have a wide variation in their predilection for the testicle. In Radin's [9] series of 4,397 cases, 611, or 13.91 per cent, of the patients had orchitis. Bailey and Haerum [10] have reported 110 cases of orchitis in 551 patients with mumps, an incidence of 19.9 per cent. Potter and Bronstein [11] noted 13 cases of orchitis in 112 adults. Dermon and Le Hew [12] found 44 cases of orchitis, or 35 per cent, in 126 men. McGuinness and Gall [13] reported 494 cases of orchitis, or 36.2 per cent, in 1,364 patients with mumps at Camp McCoy, Wis. Worden,[14] in his series, noted 41 cases, or 16.4 per cent, of orchitis in a group of 250 patients with mumps, and in the Bangs'[5] series of 74 males over 13 years of age, 49, or 66 per cent, had orchitis.

### ENCEPHALITIS

Involvement of the central nervous system is probably directly due to the virus in the same manner that encephalitis occurs in equine encephalitis, lymphocytic meningitis and poliomyelitis. Wollstein,[15] was able to produce a mild meningitis in cats by using filtered saliva from patients with mumps and injecting it suboccipitally. Gordon [16] has produced severe, and, in a few cases fatal, lymphocytic meningitis by injecting filtered mumps saliva intracerebrally into monkeys. While the involvement of the central nervous system is generally mild, Donohue [17] reported a death in a 5 year old child and reviewed the previous reports in the literature, finding 10 authenticated cases. Autopsy revealed a perivascular demyelination similar to that seen in the postinfectious encephalitides. Urechia [18] described the changes

9. Radin, M. J.: The Epidemic of Mumps at Camp Wheeler, October, 1917-March, 1918, Arch. Int. Med. **22**:354 (Sept.) 1918.

10. Bailey, W. H., and Haerum, A. T.: Some Observations on the Efficacy of Convalescent Mumps Serum, Mil. Surgeon **90**:134 (Feb.) 1942.

11. Potter, H. W., and Bronstein, L. H.: Some Clinical Characteristics of Mumps and the Effect of Belladonna in Treatment: A Study Made at the Station Hospital, Fort George G. Meade, Md., Ann. Int. Med. **21**:469 (Sept.) 1944.

12. Dermon, H., and Le Hew, E. W.: A Mumps Epidemic in a Small Task Force, Am. J. M. Sc. **208**:240 (Aug.) 1944.

13. McGuinness, A. C., and Gall, E. A.: Mumps at Army Camps in 1943, War Med. **5**:95 (Feb.) 1944.

14. Worden, E. M.: Epidemic Parotitis: An Analysis of 250 Cases in Male Adults, Canad. M. A. J. **50**:47 (Jan.) 1944.

15. Wollstein, M.: Experimental Mumps Meningitis, J. Exper. Med. **34**:537 (Dec.) 1921.

16. Gordon, M. H.: Report of the Medical Officer, Great Britain Local Gov. Public Health and Medical Subjects, London, 1914, p. 96.

17. Donohue, W. L.: The Pathology of Mumps Encephalitis with Report of a Fatal Case, J. Pediat. **19**:42 (July) 1941.

18. Urechia, C. J.: Parotidite épidémique à forme psychosique; autopsie, Encéphale **2**:144 (Sept.-Oct.) 1938.

in the rare fatal cases of encephalitis as characterized by slight lesions of nerve cells, perivascular infiltrations predominately lymphocytic, neuroglial reactions, foci with demyelination and small capillary hemorrhages. Myelitis, optic neuritis, nystagmus, neuritis and polyneuritis have been reported [19] as complications of this disease.

The terminology of the disease process involving the central nervous system is not standardized. The manifestations of fever, headache and drowsiness, associated at times with nuchal rigidity and with the presence of Kernig and Brudzinski signs, plus a positive Pandy reaction and a lymphocytic pleocytosis of the spinal fluid, have been variously called encephalitis, meningitis and meningoencephalitis. Since the same symptom complex associated with other virus diseases is classified as encephalitis, it seems proper that this manifestation should also be called encephalitis.

Since pleocytosis may occur with or without symptoms, mumps encephalitis is classified as either latent or manifest. In this asymptomatic reaction, there appears to exist the mildest form of involvement of the central nervous system. Finkelstein [20] examined the spinal fluid of 40 patients with mumps and found pleocytosis in 16. Of these, 10 had encephalitic symptoms, while 6 were asymptomatic. Cell counts varied from 15 to 1,250, mainly lymphocytes, with no correlation between the number and the severity of the symptoms. Dopter [21] reported a 9.8 per cent incidence of encephalitis among 1,705 men with mumps in the French army. Dermon and Le Hew [12] found only 1 case of encephalitis in 129 adults; Potter and Bronstein [11] noted 2 cases of encephalitis in 112 persons with mumps. Wesselhoeft [6] stated that clinical evidence of involvement of the central nervous system occurs in 10 per cent of the cases. The Bangs [8] have made an excellent study of 458 patients with mumps hospitalized in Copenhagen in the winter of 1941-1942. Examinations of the spinal fluid were made for all of the patients, and it was found that 235, or 65 per cent, showed an increased cell count. One hundred and six, or 45 per cent, revealed manifest encephalitis, while in 129, or 55 per cent, the encephalitis was latent. The time of onset of manifest symptoms was usually the fifth day, although cases were reported from as long as seven days before to thirty-eight days after involvement of the salivary glands occurred.

It can be seen that statistics for mumps encephalitis depend on the type of observation made. When diagnostic examination of the spinal fluid is made, the incidence of pleocytosis may be as high as

19. McKaig, C. B., and Woltman, H. W.: Neurologic Complications of Epidemic Parotitis, Arch. Neurol. & Psychiat. **31**:794 (April) 1934.

20. Finkelstein, H.: Meningo-Encephalitis in Mumps, J. A. M. A. **111**:17 (July 2) 1938.

21. Dopter, C.: La méningite ourlienne, Paris méd. **1**:35, 1910.

100 per cent, as in de Massary's [22] series, or when clinical symptoms alone are considered it may be as low as that recorded in Radin's [9] report, in which he noted only 1 case of encephalitis in 5,756 cases of mumps in soldiers at Camp Wheeler in 1918.

Pancreatitis is an unusual manifestation, or at least its diagnosis is rarely made. Sinclair [23] stated that only 26 cases are on record in the United States Army during the World War. Greene and Heeren [24] found 7 instances in their series of 100 adults with mumps. Brahdy and Schefer [25] reported 13 cases of pancreatitis in 252 patients, and Haerem [26] reported 6 cases of this disease in 500 patients with mumps.

Ocular complications have been described frequently.[27] Conjunctivitis, keratitis, dacryoadenitis, optic neuritis, muscular paralysis, nystagmus, neuroretinitis and disturbances of accommodation have been noted.

## CLINICAL STUDY.

An epidemic of mumps during the winter of 1945 in a specialized school of the Navy provided the material for this study. From March 1 to July 1, 1945, 249 men were admitted to the hospital with mumps. A study of the effect of convalescent serum in the prevention of associated manifestations and of the effect of convalescent serum and normal pooled plasma in the treatment of orchitis was made. Pooled serum was made from various groups of these patients by the Samuel Deutsch Serum Center of Michael Reese Hospital, blood being drawn three to six weeks after recovery. One hundred and fifty-seven of these men were 17 to 21 years of age; 80 were 21 to 30, and 12 were in the 31 to 39 year age group. These groups corresponded to the proportionate age groups of the men in the school and are not indicative

22. de Massary, E., and Tockmann, L.: Statistique portant sur 243 militaires atteintes d'oreillons, soignés á l'hôpital Andral: Fréquence des orchites et des réactions méningées, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1035, 1916.

23. Sinclair, C. G.: Mumps: Epidemiology and Influence of the Disease on the Non-Effective Rate in the Army, Mil. Surgeon **50**:626 (June) 1922.

24. Greene, J. A., and Heeren, R. H.: Mumps, J. Lab. & Clin. Med. **23**:129 (Nov.) 1937.

25. Brahdy, M. B., and Schefer, I. H.: Pancreatitis Complicating Mumps, Am. J. M. Sc. **181**:255 (Feb.) 1931.

26. Haerem, A. T.: Treatment of Measles and Mumps with Three Well Known Sulfonamides, Mil. Surgeon **92**:306 (March) 1943

27. Wesselhoeft, C., in Virus and Rickettsial Diseases, Harvard School of Public Health, Symposium, Cambridge, Mass., Harvard University Press, 1940, p. 309. Lippman, O.: Keratitis Due to Mumps, South. M. J. **36**:654 (Sept.) 1943. Danielson, R. W., and Long, J. C.: Keratitis Due to Mumps, Am. J. Ophth. **24**: 655 (June) 1941. Powell, L. S., and Dunlap, R. L.: Report of Two Cases with Visual Disturbances Complicating Epidemic Parotitis, J. Kansas M. Soc. **41**:432 (Oct.) 1940.

of age immunity. No age is considered exempt from this disease, but as the age increases more persons have had mumps, with a resulting decrease in the number of susceptible persons. In general, it can be said that one attack produces immunity, regardless of the number of glands involved, although second and even third attacks do infrequently occur.

Bilateral parotitis was noted in 112 men, unilateral parotitis in 75, parotitis and involvement of the submaxillary or sublingual glands in 54 and involvement of the submaxillary glands alone in 8. Thus, involvement of the parotid glands was present in 97 per cent of the patients, of whom 45 per cent had bilateral involvement, 30 per cent had unilateral involvement and 25 per cent had involvement of the parotid glands associated with involvement of the submaxillary and the sublingual glands. Radin's [9] figures, compiled in a study of 4,274 cases, showed involvement of the parotid glands in 99 per cent (unilateral in 59 per cent, bilateral in 30 per cent and associated with involvement of the submaxillary glands in 10 per cent). Feer [28] noted involvement of the submaxillary glands in 25 per cent of his 146 patients.

One hundred and sixty-three men constituted the control group, while 86 received convalescent serum on the first day of clinical symptoms. Serum was administered as it became available, so that the two groups were mixed throughout the months of study. Forty cubic centimeters of convalescent serum was given intravenously on admission to each of the treated patients. Orchitis occurred in 14, or 16.27 per cent, of the 86 men given serum, while it occurred in 47, or 28.83 per cent, of the 163 controls. Bilateral orchitis occurred in 2 of the treated and in 5 of the control group. Statistical analysis, employing the chi-square test, indicates that serum treatment reduced the incidence of orchitis.

Clinical symptoms of encephalitis were present in 14, or 16.27 per cent, of the 86 men of the serum-treated group and in 26, or 15.23 per cent, of the 163 controls. The diagnosis of encephalitis was made on the basis of clinical symptoms, the absence of other complicating factors and the presence of pleocytosis in the spinal fluid. Examinations of the spinal fluid were not made on asymptomatic patients, and therefore the number of patients with latent encephalitis is unknown. Four of the treated group had both orchitis and encephalitis, while 11 of the controls had both. Conjunctivitis was noted in 6 of the serum-treated group and in 7 of the controls. Presternal edema of a high degree was noted in 4 patients. It is probable that this condition

28. Feer, W.: Beobachtungen bei Parotitis epidemica, Schweiz. med. Wchnschr. **73**:1569 (Dec. 31) 1943.

would have been noted more frequently, but examinations were not made specifically for this. Gellis and Peters [29] reported its presence in 30, of 6 per cent, of 502 cases. Barker [30] noted its incidence in 3 of 438 cases. This phenomenon is explained on the basis of lymphatic obstruction by pressure of the enlarged salivary glands (table 1).

The diagnosis of pancreatitis could not be definitely made for any of the patients observed during this study.

The effect of convalescent serum on the clinical manifestations was studied. The average temperature of the treated group was 101.18 F. and of the control group 101.16 F.; the average number of days of fever of the treated group was 2.98 and of the control group 3.03. The average stay in the hospital for the treated group was 10.8 days, while for the controls it was 11.87 days.

TABLE 1.—*Clinical Manifestations in 249 Cases of Mumps*

| Patients | Orchitis | Encephalitis | Orchitis and Encephalitis | Conjunctivitis | Presternal Edema |
|---|---|---|---|---|---|
| Serum treated (86) | 14 | 14 | 4 | 6 | 1 |
| Controls (163) | 47 | 26 | 11 | 7 | 3 |

TABLE 2.—*Relationship of Involvement of Salivary Glands to Associated Manifestations*

| Glands Involved | Orchitis | Encephalitis | Orchitis and Encephalitis | Conjunctivitis | Presternal Edema |
|---|---|---|---|---|---|
| Parotid bilaterally (112) | 23 | 10 | 10 | 7 | 1 |
| Parotid unilaterally (75) | 11 | 7 | 5 | 2 | 0 |
| Parotid and submaxillary or sublingual (54) | 9 | 7 | 0 | 4 | 3 |
| Submaxillary alone (8) | 3 | 1 | 0 | 0 | 0 |

The average time of onset of orchitis was six days in each group. The average time of appearance of encephalitis in the serum-treated group was 5.8 days after onset and 4.8 days in the controls. Conjunctivitis appeared on the average of 6.2 days after onset in both groups, and symptoms were present about fourteen days in both. Presternal edema was noted on the average of six days after the onset.

A study of the associated conditions in relation to each type of involvement of salivary glands was made. The various percentages of cases of orchitis, encephalitis and conjunctivitis appear approximately proportionate to the total number of various involvements of salivary glands (table 2).

29. Gellis, S. S., and Peters, M.: Mumps with Pre-Sternal Edema, Bull. Johns Hopkins Hosp. **75**:241 (Oct.) 1944.

30. Barker, C. S.: Complication of Mumps-Swelling over Manubrium Sterni, Canad. M. A. J. **48**:22 (Jan.) 1943.

### TREATMENT OF ORCHITIS

The use of convalescent serum and plasma in the treatment of mumps orchitis was studied. Gradwohl and co-workers [31] reported excellent therapeutic results with only 5 cc. of convalescent serum in the treatment of orchitis. In 1944, I [32] reported 2 cases of mumps orchitis in which there was a dramatic response to the use of 500 cc. (1 unit) of pooled normal plasma. The temperature of each patient dropped by crisis within twenty-four hours. This report stimulated the study of Smith,[33] who had similar results in 5 cases. In the present study, there were a total of 61 cases of orchitis. In 5 of these, the patients were afebrile and were not included in the control group, since all patients who were treated with either plasma or serum were febrile. In the control group of 30 patients, the temperatures dropped by crisis in three days or less in 7 instances; a drop by lysis in three days or less was noted in 3, and in 20 men the fever defervesced by lysis in more than three days. Thirteen men were treated with

TABLE 3.—*Effect of Treatment on Orchitis*

| Patients | Temperature Dropped by Crisis in Three Days or Less | Temperature Dropped by Lysis in Three Days or Less | Temperature Dropped in More Than Three Days | Average Number Days of Fever |
|---|---|---|---|---|
| Serum treated (13) | 3 | 4 | 6 | |
| Plasma treated (10) | 6 | 1 | 3 | 4.52 |
| Serum and plasma treated (3) | 2 | 0 | 1 | |
| Controls (30) | 7 | 3 | 20 | 5.40 |

500 cc. of pooled normal plasma. In 6 the temperatures dropped by crisis in three days or less; in 1, by lysis in three days or less, and in 6, by lysis in more than three days. Ten patients with orchitis were treated with 40 cc. of convalescent serum; in 3 of these the temperatures dropped by crisis and in 4 by lysis in three days or less, while in 3 the fever lasted more than three days. Three patients were treated with 500 cc. of plasma and 40 cc. of serum, both being administered on the day of onset. In 2 of these the temperatures dropped by crisis in less than three days, and in 1 the fever lasted five days. The average number of febrile days in the treated group was 4.5 and in the untreated group 5.5. In summarizing these figures, it is found that of the treated group 16 had fever for three days or less and 10 had longer febrile courses, as compared with 10 with fever of three days or less and 20 for more than three days in the untreated group (table 3).

31. Gradwohl, R. B. H.: Study of an Epidemic of Mumps, U. S. Nav. M. Bull. **13**:723 (Oct.) 1919.

32. Rambar, A. C.: Pooled Plasma Treatment of Mumps Orchitis, U. S. Nav. M. Bull. **42**:871 (April) 1944.

33. Smith, R. G.: Plasma Treatment of Mumps Orchitis, U. S. Nav. M. Bull. **44**:159 (Jan.) 1945.

THE PROPHYLACTIC USE OF CONVALESCENT SERUM

The value of convalescent serum as a protective agent appears to be fairly well substantiated. The earliest report is that of Hess,[34] who treated 17 exposed nonimmune children with an intramuscular injection of 6 to 8 cc. each of convalescent whole blood obtained from donors who had recently recovered from mumps. The disease did not develop in any of these 17. Regan[35] administered 2 to 4 cc. of convalescent serum to each of 70 children; only 1 had mumps. Skrotzky[36] gave injections of 5 to 15 cc. of convalescent serum to 179 exposed children, of whom only 2 had mumps and their disease was mild. Zeligs[37] reported the successful protection of all 44 children in contact with the disease to whom he gave injections of 5 cc. of serum from donors recently recovered from mumps. Cambessédès[38] reported 100 per cent success, using an injection of 10 to 20 cc. of convalescent serum. Dwyer[39] obtained 100 per cent protection for 31 schoolboys by using 4 cc. of convalescent serum for each. Teissier's[40] report was similar, he having used 10 to 20 cc. of convalescent serum for each of 22 girls. Levinson and Wolfe's[41] figures showed that of 23 nonimmune persons in contact with the disease in their homes given injections of 10 cc. of convalescent serum mumps developed in 4; by using 15 cc. each in 4 susceptible persons, no mumps developed; by using 20 cc. of serum each in 157 susceptible persons, no disease appeared in 144, or there was 92 per cent success. Ruhrah[42] stated that the disease should be expected to develop in one fourth to one third of the susceptible persons in contact. Barenberg and Ostroff[43] gave 40 children in an institution 5 cc. of convalescent serum each.

34. Hess, A. F.: A Protective Therapy for Mumps, Am. J. Dis. Child. **10**:99 (Aug.) 1915.

35. Regan, J. C.: Serum Prophylaxis of Epidemic Parotitis, J. A. M. A. **84**: 279 (Jan. 24) 1925.

36. Skrotzky, A. I.: The Seroprophylaxis of Epidemic Parotitis, Odessky M. J. **4**:8, 1929; abstracted, J. A. M. A. **93**:345 (July 27) 1929.

37. Zeligs, M.: Convalescent Serum in the Prevention of Mumps, J. Pediat. **1**: 727 (Dec.) 1932.

38. Cambessédès, H.: L'emploi du sérum de convalescents dans les oreillons, Ann. d'hyg. **11**:83 (Feb.) 1933.

39. Dwyer, H. L.: Convalescent Serum in the Prophylaxis of Mumps, J. Kansas M. Soc. **25**:257 (Aug.) 1925.

40. Teissier, P.: Prophylactic Value of Convalescents' Serum in Mumps, Bull. Acad. de méd., Paris **93**:369 (April 7) 1925; abstracted, J. A. M. A. **84**:1701 (May 30) 1925.

41. Levinson, S. O., and Wolfe, A.: Personal communication to the author.

42. Ruhrah, J., in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1925, vol. 6, p. 277.

43. Barenberg, L. H., and Ostroff, J.: Use of Human Blood in the Protection Against Mumps, Am. J. Dis. Child. **42**:1109 (Nov.) 1931.

The disease developed in 39 per cent of 125 untreated controls in the same institution, while only 15 per cent of the treated group came down with mumps and these had a milder form. Gunn [44] gave injections of 5 cc. of serum to 22 susceptible persons who escaped the disease, but a few weeks later mumps developed in 3 after secondary exposures. Lyday,[45] using 10 cc. of convalescent serum, reported 11 failures to immunize in 86 children given injections. Odenius [46] reported 100 per cent success for the use of serum in men of the Swedish army, using 10 cc. in each repeated once in three to five days. Smaller amounts used before had been unsuccessful. This was noted by Vasquez [47] who used injections of 0.1 to 2.5 cc. of serum subcutaneously and had 20 failures in immunization among 175 exposed Chilean soldiers. Beeson and co-workers [48] used injections of 4.5 and 6 cc. of pooled plasma for a group of soldiers in England. Six days later 8 cc. of another plasma was given. A decrease in the incidence of mumps occurred, but this was not striking.

However, they observed that hepatitis occurred in 101 of 266 men given this serum and concluded from epidemologic studies that it was due to a hepatotoxic agent present. MacNalty [49] reported this condition in a group of children given measles convalescent serum. Morgan and Williamson [50] noted its appearance after the giving of pooled and dried reconstituted human adult serum. Whole blood transfusions have also produced it. Neefe and co-workers [51] reported its occurrence in a male physician eleven weeks after the intravenous injection of 200 cc. of pooled mumps human convalescent serum.

The administration of convalescent serum to patients with parotitis as a prophylactic measure against other manifestations has been reported by many observers. Gordon and Heeren [5] have reviewed these reports

44. Gunn, W.: Convalescent Serum in Prophylaxis of Measles, Chickenpox, and Mumps, Brit. M. J. **1**:183 (Jan. 30) 1932.

45. Lyday, J. H.: An Evaluation of Convalescent Serum in the Prevention of Mumps, J. Pediat. **18**:473 (April) 1941.

46. Odenius, R.: Attempt at Immunization Against Mumps in Royal Norrland Regiment, 1926, Tidskr. i mil. Hälsov. **51**:177, 1926.

47. Vasquez, A.: Seroprofilaxis de la parotiditis epidemica con suero de convalesciente, in Actas y trabajos de Primer congresso de medicina y cirugia naval y militar de Chile, Valparaiso, 1929, p. 675.

48. Beeson, P. B.; Chesney, G., and McFarlan, A. M.: Hepatitis Following Injection of Mumps Convalescent Plasma, Lancet **1**:814 (June 24) 1944.

49. MacNalty, A. S.: Report of the Chief Medical Officer, 1937, Great Britain Ministry of Health, London, 1938.

50. Morgan, H. V., and Williamson, D. A. J.: Jaundice Following Administration of Human Blood Products, Brit. M. J. **1**:750 (June 19) 1943.

51. Neefe, J. R.; Miller, T. G., and Chornock, F. W.: Homologous Serum Jaundice: A Review of the Literature and Report of a Case, Am. J. M. Sc. **207**:626 (May) 1944.

and have expressed the opinion that they lack proof of any worth while knowledge. Bailey and Haerum [10] studied a group of patients and noted that of 551 controls orchitis developed in 110, or 19.9 per cent, while of 183 who received 10 to 20 cc. of serum each 28, or 15.3 per cent, had orchitis. Of the 183 patients who received serum, 135 had serum from donors who had not had orchitis. The disease developed in 26, or 19.2 per cent, of these, while of the 48 who had serum from donors who had orchitis this manifestation developed in only 2, or 4.2 per cent. They suggested that blood from patients with orchitis contains specific antibodies against this condition. Teisser [52] gave 20 to 40 cc. of serum to each of 172 patients with the disease and found that orchitis developed in 8.13 per cent, while in a group of 174 controls it developed in 23.29 per cent. De Lavergne and Florentin [53] treated 113 patients with injections of 20 cc. of convalescent serum, with an additional 10 cc. five days later. Orchitis occurred in 5 instances and meningitis in 2, while in 107 controls orchitis occurred in 25 and meningitis in 9. Odenius [46] noted that of 18 patients each given 20 cc. of convalescent serum at the onset of swelling of the parotid glands orchitis developed in 1, or 5.5 per cent, while of 52 untreated patients 5, or 9.5 per cent, had this disease. Cambessédès [38] used a dose of 20 to 40 cc. of serum in 171 cases of mumps, with orchitis resulting in 7 per cent of the patients. Of 176 controls orchitis developed in 23 per cent. Iversen [54] administered 40 cc. of mumps serum to alternate persons in a group of soldiers with mumps. Of the 56 serum-treated patients, orchitis in 20 per cent developed while of the 56 controls 30 per cent were involved. Hinckley [55] noted that 13 per cent of his 23 serum-treated patients had complications as compared with 40 per cent of the 55 controls. The serum-treated patients had a shorter and milder course, with an average of 10.17 days in the hospital with 4.26 febrile days in the treated, as compared with 12.24 hospital days with six febrile days in the controls. Candel [56] used 100 cc. of pooled plasma intravenously in each of 30 patients, of whom 6, or 20 per cent, had orchitis. They concluded that 100 cc. of pooled normal plasma does not lower the

52. Teissier, P.: Epidemiology and Prophylaxis of Mumps, Bull. méd., Paris **39**:349 (March 28) 1925; abstracted, J. A. M. A. **84**:1701 (May 30) 1925.

53. de Lavergne, V., and Florentin, P.: Convalescents' Serum in Prevention of Orchitis in Mumps, Bull. Acad. de méd., Paris **93**:362 (March 31) 1925; abstracted, J. A. M. A. **84**:1701 (May 30) 1925.

54. Iversen, P.: Complications of Epidemic Parotitis and Experimental Treatment with Convalescent Serum, Ugesk. f. læger **92**:167 (Feb. 13) 1930.

55. Hinckley, R. G.: Therapeutic Use of Convalescent Serum in Mumps, Minnesota Med. **20**:227 (April) 1937.

56. Candel, S.; Wheelock, M. C., and Grimaldi, G. J.: Mumps Orchitis, with a Discussion of Plasma Prophylaxis, U. S. Nav. M. Bull. **45**:97 (July) 1945.

incidence of orchitis. Haerem [26] gave 10 cc. of serum intramuscularly to each of 100 patients with mumps in the course of a study comparing this method of therapy with the use of the sulfonamide compounds. The serum was obtained from donors who had recovered from orchitis. Thirty per cent of those receiving the serum had orchitis, while 27 per cent of the control group and only 21 per cent of the group receiving sulfonamide compounds had it. However the majority of these reports show a definite decrease in orchitis after the use of serum.

### COMMENT

Convalescent serum appears to be the best available means of preventing mumps and of decreasing the incidence of orchitis. The reports in the literature are difficult to evaluate, since varied doses of serum and means of administering it have been used, and there is no agreement on the time period when donors should be bled. Wesselhoeft [6] expressed the belief that after the symptoms are established the virus has already become attached to the cells of the involved organs and is well out of reach of antibodies supplied in the form of therapeutic serum. He questioned some favorable conclusions reported, because Bonnamour and Bardin [57] have observed equally good results from the prophylactic use of diphtheria antitoxin. At one time Wesselhoeft [58] noted 82 consecutive cases of mumps without orchitis, followed by 6 cases of orchitis among the next 18 patients with mumps. In the present group of sailors studied, the incidence of orchitis was constant throughout the study. Bailey and Haerem [10] noted that the consensus of various observers may vary because the incidence of orchitis differs with different epidemics. The severity of the epidemic does not always parallel the incidence of orchitis. In this series, the reduction of orchitis from 28.83 per cent in the control group to 16.27 per cent in the treated group, when subjected to statistical analysis, is significant. The encephalitis observed, however, is of the same order, 16 per cent in each group. The association of orchitis with meningitis, while higher than with meningitis-free patients, is not of significant magnitude. It is interesting that no differences were found between the groups in range of temperature, number of days of fever or length of stay in the hospital.

The use of serum or plasma in the treatment of orchitis did not produce the spectacular results reported for very small series. However, in 26 treated patients the temperature of 16 dropped to normal

57. Bonnamour, S., and Bardin, J.: Le sérum antidiphtérique dans le traitement des oreillons comme préventif de l'orchite ourlienne, Presse méd. **28**:929 (Dec. 22) 1920.

58. Wesselhoeft, C.: Mumps, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1941, vol. 5, pt. 2, p. 497.

in three days or less, while of 30 controls this occurred in only 10. Since the subjective feeling of illness in mumps orchitis is directly related to the fever, it would appear that these men were benefited by this procedure. Stengel [59] stated that in patients with orchitis, although the fever may end by crisis, slow subsidence, or lysis, is usually seen. Of 249 patients with mumps who were studied in this epidemic, 101 had either orchitis or manifest encephalitis or both.

There is sufficient clinical statistical evidence to show that this disease does little damage to boys below the age of puberty, and Wesselhoeft [27] is sound in his conclusion that familiarity with mumps tends to breed a respect for the advantages of early active immunity. One should weigh the few dangers of the disease in children with the great chances of serious involvements in adults before instituting protective measures in children.

## SUMMARY

1. Of 249 men with mumps, orchitis developed in 61, or 24.5 per cent. In 86, to whom 40 cc. mumps convalescent serum was given intravenously on admission, orchitis developed in 14, or 16.27 per cent. In 163 controls, orchitis developed in 47, or 28.83 per cent. These figures are significant when subjected to statistical analysis.

2. There was manifest encephalitis in 40 of the 249 patients, no difference being noted between the serum-treated patients and the control groups. In 15 instances, both orchitis and encephalitis occurred together. Thus 86, or 35.3 per cent, of the 249 patients had orchitis, encephalitis or both.

3. Convalescent serum and pooled plasma were used in the treatment of orchitis. Sixteen of the 26 treated patients had fever three days or less, the temperature of all of them dropping by crisis, as compared with a group of 30 control patients, in 10 of whom the fever lasted three days or less while in only 7 the temperature dropped by crisis. Since the total number of days of fever in the treated group averaged 4.52 as compared with 5.4 in the controls, the value of serum or plasma as a therapeutic procedure cannot be definitely demonstrated.

Dr. Sidney O. Levinson, director of the Samuel Deutsch Serum Center of Michael Reese Hospital, Chicago, gave suggestions and assisted in the preparation of these data.

1525 East Fifty-Third Street, Chicago.

59. Stengel, A., Jr.: Mumps Orchitis, Am. J. M. Sc. **191**:340 (March) 1936.

# PATHOGENESIS OF CONGENITAL HEMOLYTIC DISEASE (ERYTHROBLASTOSIS FETALIS)

## I. Theoretic Considerations

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THE discovery [1] of the Rh factor quickly attracted the attention of the medical profession because this property of human blood proved to be of clinical importance in explaining the great majority of intragroup hemolytic transfusion reactions [2] and erythroblastosis fetalis,[3] a group of disorders of the fetus and the newborn infant of common or related causation, namely, icterus gravis neonatorum, hemolytic anemia of the newborn, hydrops fetalis and certain unexplained stillbirths. In the present series of papers the discussion will be limited to erythroblastosis fetalis, which is better known as hemolytic disease of the fetus and newborn or, now that the pathogenesis of this condition is better understood, as congenital hemolytic disease.

According to the theory of Levine and others,[3a,b] in the typical case the father is Rh positive, the mother is Rh negative and the fetus is Rh positive, having inherited the Rh factor from the father. Fetal

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From the Serologic Laboratory of the Office of the Chief Medical Examiner of New York City and the Blood Transfusion Division of the Jewish Hospital of Brooklyn.

1. Landsteiner, K., and Wiener, A. S.: An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood, Proc. Soc. Exper. Biol. & Med. **43**:223 (Jan.) 1940. Landsteiner, K., and Wiener, A. S.: Studies on an Agglutinogen (Rh) in Human Blood Reacting with Anti-Rhesus Sera and with Human Isoantibodies, J. Exper. Med. **74**:309-320 (Oct.) 1941.

2. Wiener, A. S., and Peters, H. R.: Hemolytic Reactions Following Transfusions of Blood of the Homologous Group, with Three Cases in Which the Same Agglutinogen Was Responsible, Ann. Int. Med. **13**:2306-2322 (June) 1940. Wiener, A. S.: Hemolytic Reactions Following Transfusions of Blood of the Homologous Group: II. Further Observations on the Role of Property Rh, Particularly in Cases Without Demonstrable Isoantibodies, Arch. Path. **32**:227-250 (Aug.) 1941.

3. (*a*) Levine, P.; Katzin, E. M., and Burnham, L.: Isoimmunization in Pregnancy: Its Possible Bearing on the Etiology of Erythroblastosis Foetalis, J. A. M. A. **116**:825-827 (March 1) 1941. (*b*) Levine, P.; Burnham, L.; Katzin, E. M., and Vogel, P.: The Role of Iso-Immunization in the Pathogenesis of Erythroblastosis Fetails, Am. J. Obst. & Gynec. **42**:925-937 (Dec.) 1941. (*c*) Wiener, A. S.: Blood Groups and Transfusion, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1943, chap. 20.

blood gains access to the circulation of the mother and sensitizes her, and the Rh agglutinins produced by the mother pass through the placenta into the fetus and combine with the fetal Rh-positive red blood cells and thus give rise to one or another manifestation of hemolytic disease. The theory does not explain how the fetal blood gains access to the maternal circulation and why, though the combination of an Rh-negative mother with an Rh-positive fetus occurs about once in every ten pregnancies, the incidence of this disease is only about 1 in 300 deliveries. In 10 per cent of the cases the mother is Rh positive, and these exceptional cases have been attributed to differences in the Rh blood types (because it is now known that there are three Rh factors instead of one) or to the Hr factor or to isoimmunization to the factors A and B.[4] With regard to the last-mentioned possibility, it is not clear why isoimmunization to A and B should so rarely cause hemolytic disease, because A and B are far better antigens than Rh for man,[5] and it does not seem reasonable to ascribe it to the protective action of the A and B substances in secretions of the fetus, because as many as 15 per cent of all persons are nonsecretors.[6] Levine's theory does not explain why in many cases of hemolytic disease in which the mother is Rh negative, no Rh agglutinins could be detected in the maternal serum or why in a number of cases in which the maternal serum contained Rh agglutinins the infant was normal though Rh positive.

The recent discovery of additional varieties of Rh antibodies[7] besides the Rh agglutinins makes it possible to explain these apparent paradoxes. The purpose of the present paper is to present a more comprehensive theory of the pathogenesis of congenital hemolytic disease, based on these newer investigations, with special reference to the role of the properties A and B.

Before presenting the theory, it is necessary to describe the different in vitro methods that have been developed for detecting Rh sensitization.

## IN VITRO METHODS OF DETECTING RH SENSITIZATION

*Agglutination Test.*[8]—When one is testing for Rh agglutinins, the usual practice is to mix a drop of the patient's serum with a drop of a 2 per cent suspension

4. Wiener, A. S.: The Rh Blood Types and Some of Their Applications, Am. J. Clin. Path. **15**:106-121 (March) 1945.

5. Wiener, A. S.; Soble, R., and Polivka, H.: Simple Method of Preparing Potent Blood Grouping Sera, Proc. Soc. Exper. Biol. & Med. **58**:310-312 (April) 1945.

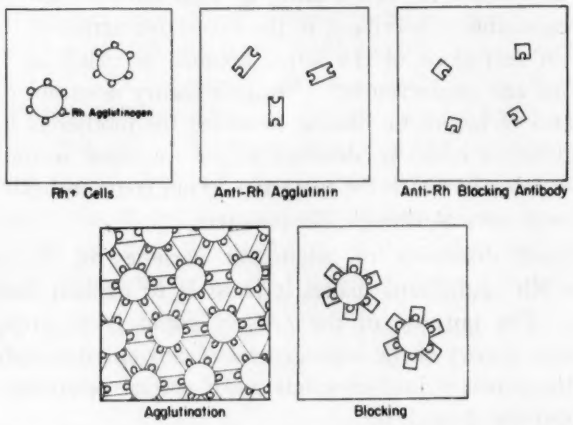
6. Wiener,[3c] p. 328.

7. Wiener, A. S.: (*a*) A New Test (Blocking Test) for Rh Sensitization, Proc. Soc. Exper. Biol. & Med. **56**:173-176 (June) 1944; (*b*) Conglutination Test for Rh Sensitization, J. Lab. & Clin. Med. **30**:662-667 (Aug.) 1945.

*(Footnotes continued on next page)*

of known Rh-positive cells in isotonic solution of sodium chloride in a narrow tube, and incubate the mixture in a water bath at body temperature for thirty to sixty minutes. (Since there are several varieties of Rh agglutinins,[9] it is well to set up tests against Rh-positive cells of types $Rh_1$ and $Rh_2$, while Rh-negative test cells are included as a control.) Their reactions are read by inspecting the appearance of the red cell sediment, and then the tube is *gently* shaken to dislodge the sediment, and the mixtures are examined with the naked eye or under the low power lens of the microscope for the presence or absence of clumping. When only weak agglutinins are present, centrifugation of the mixture may be necessary to bring out the reaction; when potent agglutinins are present, prompt agglutination may occur even in tests carried out by the slide technic at room temperature or by the tube technic with the patient's serum highly diluted with saline solution.

Rh agglutinins, like other antibodies, are presumably modified globulins. There is also reason to believe that the Rh agglutinins as well as agglutinins for other antigens in red cells or bacteria are bivalent,




Diagrammatic representation of the Rh agglutination and Rh blocking reactions.

that is, the antibody molecule contains more than one combining group for the specific antigen. Thus, when antigen and antibody combine, agglutination results through the formation of a latticework,[10] as shown in the chart. As will presently be seen, this concept of the nature of the agglutination reaction is helpful in explaining the pathogenesis of congenital hemolytic disease.

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8. Wiener, A. S.: Hemolytic Transfusion Reactions: III. Prevention, with Special Reference to the Rh and Cross-Match Test, Am. J. Clin. Path. **12**: 302-311 (June) 1942.

9. Wiener, A. S.: The Rh Blood Factors, J. A. M. A **127**:294 (Feb. 3) 1945.

10. Marrack, J. R.: The Chemistry of Antigens and Antibodies, Medical Research Council, Special Report Series, no. 230, London, His Majesty's Stationery Office, 1938. Wiener, A. S., and Herman, M.: Second Stage of the Agglutinative Reaction, J. Immunol. **36**:255-259 (April) 1939.

*Blocking Test.* (*Wiener* [7a]).—If the mixture of patient's serum with Rh-positive cells shows no agglutination, then a drop of a good anti-$Rh_0$ agglutinating serum should be added to the mixture, which is then reincubated for an additional thirty to sixty minutes at body temperature. If the patient's serum contains no Rh antibodies, then the Rh-positive cells should be clumped by the anti-$Rh_0$ agglutinins; if no agglutination occurs or if the clumping is definitely weakened, then this indicates the presence in the patient's serum of Rh antibodies of a special sort. The antibodies in question combine specifically with Rh-positive blood cells but without producing a visible reaction. However, Rh-positive cells treated with these special antibodies lose their capacity of being agglutinated even by potent anti-$Rh_0$ agglutinating serums, as if they had been converted into Rh-negative cells. Evidently all the combining sites on the red cells are occupied and blocked by the special Rh antibodies, and that is the reason for the name "blocking antibodies" (see the chart).

It seems reasonable to assume that blocking antibodies, which are univalent, are therefore simpler chemical structures than agglutinins, which are polyvalent. Accordingly, it follows that it should be possible for Rh antibodies to traverse the placental barrier into the fetal circulation more readily and earlier in pregnancy than Rh agglutinins.[11] This would explain why the serums of mothers delivering stillborn erythroblastotic infants almost invariably, if not always, contain blocking antibodies, and it is evident that the presence of blocking antibodies in the maternal serum may be of graver significance than the presence of agglutinins.[12] These observations explain, at least in part, the lack of correlation between the titer of Rh agglutinins in the maternal serum and the severity of the hemolytic disease in the infant as discussed previously.

*Conglutination Test* (*Wiener* [7b]).—In cases of congenital hemolytic disease due to the Rh factor in which no Rh agglutinins are detectable in the maternal serum, Rh antibodies are, nevertheless, almost invariably, if not always, demonstrable by the conglutination technic. The technic of this test differs from that of the agglutination test merely in the avoidance of the use of saline solution or any crystalloid solution, in order to avoid dilution of the plasma or serum. The patient's serum is tested undiluted, or if diluted, as in titrations, group AB inactivated serum is used as the diluent in place of saline solution. Also, the test cell suspensions are diluted to proper strength (2 per cent in terms of blood sediment) in group AB serum instead of saline solution. In

11. Baar, H. S.: The Race-Wiener Test in Haemolytic Disease of the Newborn, Nature, London **155**:789-790 (June 30) 1945. Wiener.[7b]

12. Wiener, A. S.: Unpublished observations; footnote 7a.

other essential details the technic of the tests does not differ from that of the agglutination test.

The conglutination test differs from the agglutination test in that the former reaction proceeds in two stages instead of one because a third component, analogous to but distinct from the complement, is required for the reaction to occur. In the first stage of the reaction the Rh haptens on the red cells combine with the specific Rh antibody in the serum but without producing a visible reaction. The specifically sensitized cells then adsorb onto their surfaces the third component, which is a colloidal substance present in all normal serums, and as a result the erythrocytes stick together in clumps indistinguishable from the clumps of ordinary agglutination reactions. The colloidal substance necessary for the conglutination reaction is almost surely identical with the so-called X protein described in detail by Pedersen.[13] The X protein makes up 20 to 50 per cent of the total proteins in the plasma and is composed of large molecules consisting of aggregates of albumin, globulin and phospholipid. The X protein dissociates on slight dilution of the plasma with water, which explains the importance of avoiding the use of saline solution when performing conglutination tests.

The difference between the Rh agglutination and the Rh conglutination reactions can therefore be summarized as follows:

$$\left\{\begin{array}{l}\text{Rh-positive red cells}\\ \\ \text{Rh antigen)}\end{array}\right\} + \left\{\begin{array}{l}\text{Rh agglutinins}\\ \text{(bivalent}\\ \text{antibodies)}\end{array}\right\} \longrightarrow \text{Agglutination}$$

$$\left\{\begin{array}{l}\text{Rh-positive cells}\\ \\ \text{(Rh antigen)}\end{array}\right\} + \left\{\begin{array}{l}\text{Rh (glutinins}\\ \text{(univalent}\\ \text{antibodies)}\end{array}\right\} + \left\{\begin{array}{l}\text{X protein}\\ \\ \text{(conglutinin)}\end{array}\right\} \longrightarrow \text{Conglutination}$$

It is not yet certain whether the specific antibodies responsible for the conglutination reaction are identical with the blocking antibodies or whether they represent a third variety of antibody. For convenience, in this paper, I shall refer to these antibodies as glutinins, with the understanding that the use of this term does not necessarily imply the correctness of the latter hypothesis.

With the aid of the conglutination test or Diamond and Abelson's slide test,[14] which, as I [7b] have shown, depend on the same phenomenon, it is possible to demonstrate the presence of Rh antibodies in the serum of every, or practically every, Rh-negative person who is sensitized to the Rh factor. It is evident, therefore, that these tests are invaluable for clinical diagnostic use, because a negative reaction in the conglutination tube test or the slide test practically rules out the presence of Rh sensitization, even though the patient is Rh negative. Since glutinin

13. Pedersen, K. O.: Ultracentrifugal Studies on Serum and Serum Fractions, Boktryckeri-A.-B., Uppsala, Sweden, Almqvist & Wiksells, 1945.

14. Diamond, L. K., and Abelson, N. M.: The Demonstration of Anti-Rh Agglutinins: An Accurate and Rapid Slide Test, J. Lab. & Clin. Med. **30**:204-212 (March) 1945.

cannot bring about clumping of the red cells without the aid of X protein, one may assume that glutinin, like blocking antibody, is univalent and therefore comprised of small molecules. Glutinin and/or blocking antibody, therefore, are far more important than agglutinin in relation to the pathogenesis of congenital hemolytic disease, because of the greater ease with which the former can pass through the placenta.[15]

It is clear now that blood group incompatibility of the fetus's blood cells for the maternal serum does not ordinarily give rise to hemolytic disease, because the natural isoagglutinins anti-A and anti-B, like Rh agglutinins, are polyvalent and probably large molecular structures, so that they do not traverse the placenta readily.[16] Moreover, even when the titer is specifically increased by isoimmunization, the immune anti-A and anti-B bodies will frequently be agglutinins rather than glutinins; therefore, the frequency of cases of congenital hemolytic disease due to A-B-O incompatibility would not be expected to be much greater than that of cases of the disease due to Rh incompatibility. When one considers that the group-specific substances A and B are present in alcohol-soluble form in most of the tissues of the body in addition to the red cells in nonsecretors as well as in secretors, it is evident that the fetal red cells are better protected from maternal glutinins in cases of A-B-O incompatibility than in cases of Rh incompatibility. It is not surprising, therefore, that in cases of hemolytic disease due to A-B-O incompatibility the signs and symptoms are usually mild or subclinical and that recovery is the rule, either spontaneous or after one or two transfusions, as will be described in a later paper in this series.[17]

Another peculiar feature of congenital hemolytic disease, namely, that infants apparently normal at birth suddenly manifest jaundice and anemia one or more days afterward, can reasonably be explained through the new knowledge of X protein. Presumably, X protein is usually not fully developed in the fetus, but shortly after birth, with its attendant profound physiologic and biochemical changes, X protein forms from its various components, albumin, globulin and phospholipid, in the plasma. As soon as sufficient X protein becomes available, the infant's red cells, already specifically sensitized by maternal glutinin acquired through the placenta antenatally, begin to break down. In cases in which sufficient X protein is formed antenatally or in which the amount of glutinin derived from the mother is so great that the breakdown of fetal cells occurs even without the aid of X protein, the disease

15. Glutinins have been demonstrated in the serums of erythroblastotic infants for periods up to a month (Wiener [7b]).

16. Wiener, A. S., and Silverman, I. J.: Permeability of the Human Placenta to Antibodies: Quantitative Study, J. Exper. Med. **71**:21-27 (Jan.) 1940.

17. Wiener, A. S.: To be published.

may start in utero and a stillbirth result. In support of these ideas may be mentioned the observations of Pedersen, who found in the plasma of cow's fetuses or of newborn calves and foals a globulin of low molecular weight, named "fetuin" by him and believed by him to be one of the precursors of X protein. Fetuin was also found in human umbilical cord blood, though in only small amounts.

### THEORY OF PATHOGENESIS OF CONGENITAL HEMOLYTIC DISEASE

Natural antibodies for the Rh factor have never been convincingly demonstrated in the plasma of Rh-negative persons never previously exposed to the Rh factor, and the natural anti-A and anti-B isoantibodies, as already explained, are agglutinins and not glutinins. For sensitivity to Rh, A, B or any other blood factor to develop, the person must first be exposed to the antigen in question. In cases of Rh sensitization, such exposure could occur either through a previous transfusion of Rh-positive blood or through pregnancy with an Rh-positive fetus. Similarly, in cases of sensitization to the factors A and B, this could result from a transfusion of plasma or from a pregnancy with a fetus of an incompatible blood group. The fact that congenital hemolytic disease only rarely occurs at a first pregnancy unless the mother has received a previous transfusion suggests that there is hardly ever any opportunity for leakage of fetal blood into the maternal circulation during pregnancy but that this occurs mainly at parturition, owing to disturbances at the placental site during labor and delivery. In support of the idea is the observation that in sensitized persons the anti-Rh titer only rarely changes during pregnancy but that a rise in titer frequently is observed seven to ten days after delivery.

The opportunities for Rh and A and B sensitization to occur are far more frequent than the number of cases of congenital hemolytic disease or intragroup transfusion reactions. This suggests that in addition to exposure to the specific antigens a constitutional factor, which may be designated by the symbol K, is required, which confers on the patient the ability to respond to such exposure by the production of specific glutinins and/or other sensitizing antibodies. The constitutional factor K appears to be genetically determined, so that an Rh-negative sister of a woman who has had infants with hemolytic disease is far more apt to become sensitized to the Rh factor on suitable exposure than another Rh-negative woman without such a family history.[18]

18. Wiener, A. S.: Unpublished observations. Unger, L. J., and Wiener, A. S.: Observations on Sensitization to the Rh Factor by Blood Transfusion, Am. J. Clin. Path. **15**:280-285 (July) 1945. Waller, R. K.; Levine, P., and Garrow, I.:

Aside from differences among individuals with regard to their capacity to become sensitized, there are also differences among the blood factors in their antigenic action. Thus, A and B are by far the best antigens for man, while $Rh_o$ is a weaker antigen. Still weaker antigens are the factors Hr, Rh′ and Rh″ and such antigens as P, M and O, while factor N has never been found to stimulate the production of isoantibodies in man.[19] These differences in antigenicity explain some of the apparent paradoxes in congenital hemolytic disease, particularly when the fetal red cells contain more than one blood factor absent from the mother's blood cells, in which case the principle of competition of antigens would come into play.[20] According to this principle, when an animal receives injections of two antigens simultaneously, the more potent antigen tends to suppress the antigenicity of the less active one. Thus, if an Rh-negative woman of group O possessing the constitutional factor K bears a group A, Rh-positive fetus, she may react either by producing anti-A glutinins without anti-Rh glutinins or, if more strongly sensitized, by producing both anti-Rh and anti-A glutinins, but she would never, or hardly ever, produce anti-Rh glutinins alone. Since anti-A and anti-B glutinins appear to be less harmful to the fetus than anti-Rh glutinins, an Rh-negative woman is slightly better off with a husband in an incompatible group and Rh positive than with a husband who is in a compatible blood group and Rh positive.

The manifold clinical manifestations of congenital hemolytic disease may be correlated with variations in the quantity and quality of the antibodies in the maternal serum. When a good deal of antibody passes into the fetal circulation during the pregnancy, a stillbirth is apt to result; on the other hand, if the antibodies in the maternal serum are weak and appear late in pregnancy, the infant will usually be born alive. In the latter event, when the maternal serum contains univalent antibodies (glutinins) the infant will usually be "pale," owing to the development of a hemolytic anemia, a condition which responds, as a rule, to proper transfusion therapy. On the other hand, if the maternal serum contains bivalent antibodies (agglutinins), the infant will often be "toxic," owing to the formation of agglutination thrombi with resulting hepatic damage and kernicterus; fortunately, such infants only rarely survive. Incidentally, the suggestion that modern transfusion therapy may serve only to save infants for a worse fate—mental

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Case of Erythroblastosis Caused by Immunization of an Rh-Positive Mother by the Rh Factor, ibid. **14**:577-581 (Nov.) 1944.

19. Wiener, A. S., and Unger, L. J.: Isoimmunization to Factor P by Blood Transfusion, Am. J. Clin. Path. **14**:616-618 (Dec.) 1944.

20. Wiener, A. S.: Competition of Antigens in Isoimmunization by Pregnancy, Proc. Soc. Exper. Biol. & Med. **58**:133-135 (March) 1945.

deficiency—is therefore misleading; in my experience every one of approximately 20 infants cured by such treatment has developed into a perfectly normal child.

### SUMMARY OF FACTORS CAUSING HEMOLYTIC DISEASE

The observations discussed in this paper demonstrate that the pathogenesis of hemolytic disease depends on a complex of factors that can now be summarized as follows:

1. *Maternal Factors.*—(*a*) Capacity to Sensitize: As the simplest possible hypothesis, one could postulate that the ability to become sensitized, K, is transmitted genetically by a pair of allelic genes, *K* and *k*. If it is assumed, on the basis of the available statistics on the incidence of erythroblastosis, that approximately 97 per cent of all persons do not bear the gene *K*, or belong to genotype *kk*, then about 3 per cent belong to genotype *Kk*, while only rare persons (about 0.02 per cent) are homozygous for gene *K*. Almost all mothers with infants having hemolytic disease would therefore belong to genotype *Kk*. Presumably, the difference between normal (genotype *kk*) persons and those bearing gene *K* is mainly one of degree; hence the former can probably also be sensitized on sufficient exposure, e. g., ten or more pregnancies or numerous transfusions. On the other hand, the rare persons of genotype *KK* would presumably be extremely easy to sensitize. Thus, such persons could account for the rare exceptions to the rule that hemolytic disease does not occur in the first pregnancy unless the mother has been previously sensitized by blood transfusions.

(*b*) Blood Group and Type: Since the mother cannot be sensitized against blood properties present in her own erythrocytes, the blood group and Rh type of the mother would affect the chance of her having an erythroblastotic infant. For example, group O Rh-negative women could be sensitized against factors A, B, $Rh_0$, Rh′ and Rh″. On the other hand, a woman of group AB, type $Rh_1Rh_2$ would be practically immune even though homozygous for K.

2. *Fetal Factors.*—(*a*) Blood Group and Type: The most important fetal factors affecting the susceptibility of the fetus to hemolytic disease are its blood group and type. If the fetus has no blood factor lacking from its mother's blood, it is safe from the dangers of maternal isoimmunization, e. g., a group O Rh-negative infant could not contract congenital hemolytic disease. If the fetus has not yet been born, its probable type can be determined indirectly by testing the father's blood and the blood of any siblings who may be alive. For example, if the mother belongs to group O and is Rh negative, and the father to group AB, type $Rh_1$ and is Hr negative, then the expected infant must belong to either group A or group B and type $Rh_1$ (or, rarely,

to type Rh′). The likelihood that hemolytic disease will develop also depends on which blood factors the fetus has that are lacking from the maternal blood. Thus, when the mother is Rh negative and has K and the infant has blood factor $Rh_o$ (type $Rh_1$, $Rh_2$, $Rh_1Rh_2$ or $Rh_o$), the disease is most apt to develop. If an Rh-positive mother has K and belongs to group O and the fetus belongs to group A or group B, hemolytic disease is also likely to develop because of A-B incompatibility but in a milder or even a subclinical form. When mother and infant belong to the same blood group but the mother belongs to type $Rh_2$ and the infant to type $Rh_1$, or vice versa, hemolytic disease is not likely to develop, because the factors Rh′ and Rh″ are much weaker antigens than $Rh_o$. The rare instances in which these combinations have given rise to infants with hemolytic disease could be explained by assuming that the mother was homozygous for K, genotype *KK*, and therefore very easy to sensitize, and this could also account for the rare cases of hemolytic disease due to Hr sensitization.

(*b*) Development of Serum Proteins: As already pointed out, the other fetal factor influencing the severity of hemolytic disease is the stage of development of its serum proteins, in particular, X protein. Genetic and environmental factors may possibly give rise to differences in the time when X protein matures.

3. *Paternal Factors.*—Since the infant's blood is not always available for examination, it is necessary to point out that by determining the father's blood group and Rh type it may be possible to deduce what the infant's blood group and type must have been. Obviously, if the husband and wife belong to the identical blood group and Rh type, no difficulty will result. In cases in which the wife is Rh negative and the husband is Rh positive, the outlook is less favorable when the husband is homozygous (type $Rh_1Rh_2$, or Hr negative) than when he is heterozygous. In the former case, every infant must be Rh positive; hence there is a greater chance that sensitization will develop, and once the mother has become sensitized every subsequent infant will be affected. When the husband is heterozygous, on the other hand, even after sensitization has developed there is still a 50 per cent chance that the mother will have a normal infant. Similar reasoning applies in cases of A-B-O sensitization.

4. *Environmental and/or Accidental Factors.*—Among the environmental or accidental factors which influence the development of congenital hemolytic disease, the most important is the number of transfusions the mother has received. As already mentioned, a transfusion of Rh-positive blood to an Rh-negative woman may ruin her chances of ever having a viable child. It is therefore important that every woman of child-bearing age, and even young girls in pediatric services at hospitals, be tested for the Rh factor before they are given blood

transfusions. Opportunities to become sensitized to the A and B factors could arise not only from transfusions of pooled human plasma but also from therapeutic injections of tetanus antitoxin or inoculation with diphtheria toxin-antitoxin mixtures, because horse serum frequently contains the A and B factors.[21] Fortunately, however, A and B sensitization does not seem to be as serious for the fetus as Rh sensitization, though Levine [22] has expressed the belief that the former may be an important cause of repeated abortions.

In conclusion, it should be mentioned that the state of nutrition of the mother probably affects her ability to become sensitized, and other unknown factors, for example, estrogenic, intercurrent infections (competition of antigens), also probably modify the development of sensitization.

SUMMARY

The discovery of new varieties of Rh antibodies, namely, Rh blocking antibodies or Rh glutinins, has served to explain certain paradoxes in the pathogenesis of congenital hemolytic disease. These antibodies appear to consist of smaller molecules than agglutinins, and they therefore traverse the placental barrier more readily into the fetal blood stream and so are more important clinically than the agglutinins. It is postulated that the ability of the mother to become isoimmunized and produce glutinins is conditioned by a certain constitutional factor, K, in addition to exposure to the foreign antigen in the fetus's blood or as a result of transfusions of blood or plasma. Under the simplest possible hypothesis, the constitutional factor K is transmitted by a pair of allelic genes, *K* and *k*, and there is evidence that about 97 per cent of the population belong to genotype *kk* (difficult to sensitize), 3 per cent to genotype *Kk* (moderately easy to sensitize) and only rare persons to genotype *KK* (extremely easy to sensitize). With the aid of this hypothesis, an attempt has been made to account not only for cases of hemolytic disease caused by the Rh factor but also for those due to A–B–O incompatibility and the rare cases caused by sensitization to such factors as Hr, Rh′ and Rh″.

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21. Davidsohn, I.: Isoagglutinin Titers in Serum Disease, in Leukemias, in Infectious Mononucleosis and After Blood Transfusions, Am. J. Clin. Path. **8**:179-196 (March) 1938.

22. Levine, P.: Serological Factors as Possible Causes in Spontaneous Abortions, J. Hered. **34**:71-80 (March) 1943.

# PATHOGENESIS OF CONGENITAL HEMOLYTIC DISEASE (ERYTHROBLASTOSIS FETALIS)

## II. Illustrative Case Histories of Rh Sensitization

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IN THE preceding paper, a comprehensive hypothesis of the pathogenesis of congenital hemolytic disease was proposed.[1] In this paper, we shall present a number of illustrative case histories in which sensitization to the Rh factor was the cause of the disease, and at the same time we shall indicate the application of the hypothesis as an aid in the diagnosis, prognosis and treatment of the disease. The cases presented here make up only a small fraction of our clinical material, but they are representative of the various problems that may be encountered when treating congenital hemolytic disease.

### REPORT OF CASES

CASE 1.—This patient was referred to us by Dr. B. Merriam, with the history that she was in the eighth month of pregnancy and that no fetal heart sounds had been audible for the past three weeks. This was the patient's third pregnancy. The first pregnancy had terminated with the birth of a normal girl, now 4 years of age, while the second pregnancy had resulted in a 7 month macerated fetus.

The blood-grouping tests yielded the following information:

| Blood of | Group and Subgroup | MN Type | Rh Type | Hr Reaction |
|---|---|---|---|---|
| Husband | O | MN | $Rh_1$ | Negative |
| Patient (wife) | $A_2'$ | M | Negative | Positive |
| Daughter (4 years) | $A_2$ | M | $Rh_1$ | Positive |

Tests of the patient's serum did not reveal the presence of any Rh agglutinins. However, the serum had an Rh blocking titer of 2 units, while the tube conglutination test gave positive reactions in dilutions as high as 1:50.

*Interpretation.*—The first pregnancy in this case resulted in a normal child because the patient had not yet become sensitized to the Rh factor. But it was this pregnancy which made the patient sensitive and caused the appearance of univalent Rh antibodies in her serum. As was pointed out in the previous paper, blocking antibodies appear to be of more serious prognostic import than anti-Rh agglutinins. The husband's blood is Hr

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1. Wiener, A. S.: Pathogenesis of Congenital Hemolytic Disease (Erythroblastosis Fetalis): I. Theoretic Considerations, Am. J. Dis. Child., this issue, p. 14.

negative; hence he is presumably homozygous for the $Rh_1$ gene; therefore, every pregnancy had to result in a Rh-positive fetus. The second pregnancy resulted in a stillborn fetus, owing to the destructive action on the fetus's blood of the maternal univalent Rh antibodies which passed through the placenta. For the same reason, death of the fetus in utero was also inevitable during the third (present) pregnancy.

One week after the blood tests were carried out, the patient delivered a macerated fetus. After the delivery there was a severe hemorrhage, and the patient was given a transfusion of plasma. Were it not for the knowledge of the Rh factor, this patient might have been given a transfusion of Rh-positive blood, with disastrous results. This is especially true because her serum contained no Rh agglutinins, and univalent antibodies are not detectable in the ordinary direct matching tests.

Since the husband is homozygous, the prognosis for this couple for future pregnancies is practically hopeless.

CASE 2.—A young woman's first pregnancy resulted in an unexplained stillbirth. She was referred to us by her physician to find out whether the Rh factor had any bearing on this problem. Results of blood tests were as follows:

| Blood of | Group and Subgroup | MN Type | Rh Type |
|---|---|---|---|
| Husband | O | MN | $Rh_1$ |
| Patient (wife) | O | M | Negative |

The patient's serum did not contain any anti-Rh agglutinins, but it did contain Rh blocking antibodies of a titer of 10. This explained the stillbirth, but it was not clear how the patient had become sensitized to the Rh factor, as she had never received a blood transfusion. On being questioned further, she recalled that ten to twelve years previously she had been exposed to measles and was given an intramuscular injection of her mother's blood, the then current method of prophylaxis. The supposition that this was the source of the sensitization was confirmed when tests of the mother showed her to be Rh positive (group O, type $Rh_2$).[2] Ironically, the patient and her mother recalled that one of us (W.) had given the injection at their pediatrician's request.

This case demonstrates that not only transfusions of blood but also intramuscular injections of small amounts of Rh-positive blood may be sufficient to produce Rh sensitization and therefore ruin a woman's chances of having a viable child. Fortunately, this method of prophylaxis has been almost entirely replaced by more effective methods, which do not entail the injection of whole blood.

CASE 3 A.—A patient presented the following history:

Her first pregnancy (1938) resulted in the birth of a normal girl.

Her second pregnancy resulted in a stillbirth. The patient had felt life up to the end of the ninth month, and she was in labor for two days at home. The infant died during the period of labor.

2. Blood of types $Rh_1$ (or $Rh_o'$) and $Rh_2$ (or $Rh_o''$) have in common the factor $Rh_o$.

The patient desired advice because her physician was concerned that the same difficulty might recur with her third pregnancy.

Results of blood tests on the patient and her family were as follows:

| Blood of | Group and Subgroup | MN Type | Rh Type | Hr Reaction |
|---|---|---|---|---|
| Husband | $A_1$ | M | $Rh_1$ | Negative |
| Patient (wife) | $A_1$ | MN | Negative | Positive |
| Daughter (7 years) | $A_1$ | M | $Rh_1$ | Positive |

These results support the diagnosis of neonatal death due to congenital hemolytic disease, except that no Rh antibodies could be demonstrated in the patient's serum by the tube agglutination, blocking or conglutination tests. However, the absence of Rh antibodies from the patient's serum did not necessarily rule out congenital hemolytic disease, because the antibodies might have disappeared in the long interval since the last pregnancy.

CASE 3 B.—Further light was thrown on the problem just presented when an older sister of the patient of case 3 A presented the following obstetric history:

The first pregnancy terminated as an ectopic gestation.

The second pregnancy (1931) resulted in the birth of a normal boy.

The third pregnancy terminated with a miscarriage in the fourth month.

The fourth pregnancy (1933) ended with the birth of a girl who lived only ten days despite blood transfusion therapy.

The fifth pregnancy (1934) terminated with a stillbirth at seven months.

The sixth pregnancy (1938) resulted in a stillbirth at nine months.

*Results of Blood Tests.*—Only the patient's blood was available for testing in this case, and she proved to be group B, type MN, and Rh negative. Despite the interval of seven years since the patient's last pregnancy, Rh agglutinins and blocking antibodies were readily demonstrable in her serum. It is clear that the neonatal death in 1933 and the stillbirths in 1934 and 1938 were all caused by congenital hemolytic disease.

These observations in case 3 B support the conclusion that case 3 A is also one of congenital hemolytic disease, because the patients in these 2 cases are sisters. Inasmuch as the husband in case 3 A belongs to type $Rh_1$ and is Hr negative, the expected child almost surely will belong to type $Rh_1$, and hemolytic disease would therefore be expected to develop. This, then, is a good case in which to test the theory that Rh sensitization may be prevented by counterimmunization with potent, harmless vaccine.[3] Starting with the second month of pregnancy, this patient was given a course of injections of diluted typhoid and pertussis vaccines. She subsequently gave birth to a girl who was perfectly normal, though Rh positive as predicted.

CASE 4.—We were requested to see a 4 day old boy at the Shore Road Hospital, service of Dr. E. Ariola, because the infant had jaundice and anemia. The patient's mother had had only one previous pregnancy, which had resulted in a

3. Wiener, A. S.: Competition of Antigens in Isoimmunization by Pregnancy, Proc. Soc. Exper. Biol. & Med. **58**:133 (Feb.) 1945.

normal boy, now 4½ years old. Examination revealed a deeply jaundiced infant with an enlarged spleen and liver and a severe anemia (hemoglobin concentration, 40 per cent); thus there seemed little doubt that he had congenital hemolytic disease. Inasmuch as facilities for Rh typing were not at hand, blood was drawn from the mother, and the washed cells from 80 cc. of her blood were immediately transfused through an incision at the infant's ankle into the internal saphenous vein.

*Results of Grouping and Rh Tests.*—On the following morning, blood tests were carried out with the following results:

| Blood of | Group and Subgroup | MN Type | Rh Type |
|---|---|---|---|
| Father | O | M | $Rh_2$ |
| Mother | $A_1$ | M | Negative |
| Brother (4½ years) | $A_1$ | M | $Rh_2$ |
| Patient | O | M | $Rh_2$ |

No anti-Rh agglutinins could be detected in the maternal serum, but weak blocking antibodies were present. These tests therefore confirmed the diagnosis of hemolytic disease of the newborn.

*Course.*—On the day following the first transfusion of washed maternal red cells, the hemoglobin rose to 60 per cent, and a second transfusion was given from a group A (subgroup $A_2$) Rh-negative professional donor. Following this, the hemoglobin rose to a peak of 85 per cent and then gradually fell. By the second day after birth, the patient's blood was typed as Rh negative, indicating that all his own blood cells had disappeared from his circulation and that he was surviving only by virtue of the blood he had received by transfusion. For a period of more than a month thereafter, no trace of Rh-positive blood could be detected in the patient's circulation. It was necessary to give three additional transfusions from group O, Rh-negative donors before reticulocytes finally appeared in the blood smears and full recovery followed.

This case is therefore similar to others previously observed in that there was a long interval during which none of the infant's own blood cells were present in his circulation. As has been pointed out in a previous paper,[4] this can be explained by postulating either (1) that there is a temporary aplasia of the infant's bone marrow or (2) that the bone marrow delivers red blood cells in a normal fashion but these are promptly destroyed by Rh antibodies persisting in the infant's circulation. That the latter is the correct explanation will be seen from case 5.

In the present case, the groups and MN types were such that by the method of differential agglutination it was possible to follow the survival of the blood received from each donor. It was found that the mother's blood and that of the first professional donor survived the usual length of time (about two months), even though these donors both belonged to group A and their blood was therefore theoretically incompatible with that of the infant, who belonged to group O. It is well known that the antibody-producing mechanism is not fully

4. Wiener, A. S.; Wexler, I. B., and Gamrin, E.: Hemolytic Disease of the Fetus and the Newborn Infant, with Special Reference to Transfusion Therapy and the Use of the Biologic Test for Detecting Rh Sensitivity, Am. J. Dis. Child. **68**:317 (Nov.) 1944.

developed during the neonatal period and that infants depend on antibodies derived from the mother by placental transfer for their immunity. Accordingly, the infant's serum will never contain antibodies capable of reacting with the mother's red cells, and the precept that infants with hemolytic disease can always be treated by transfusions of mother's washed cells holds even when the mother's blood group is incompatible with that of the infant.

CASE 5.—We were requested to see a 3 day old girl with the following clinical history. On the second day of life the patient became jaundiced and her hemoglobin concentration was found to be 77 per cent. By the time we saw her, the hemoglobin concentration had fallen to 70 per cent. The patient was the second child. The mother's first pregnancy, which occurred three and one-half years ago, had resulted in a normal child.

*Results of Blood Grouping and Rh Tests.*—The blood tests confirmed the impression that the infant was suffering from congenital hemolytic disease.

| Blood of | Group and Subgroup | MN Type | Rh Type | Hr Reaction |
|---|---|---|---|---|
| Father | B | M | $Rh_1$ | Positive |
| Mother | O | N | Negative | Positive |
| Brother | O | MN | $Rh_1$ | Positive |
| Patient | O | MN | $Rh_1$ | Positive |

Tests on the maternal serum showed no Rh agglutinins by the usual tube technic and only weak blocking antibodies. The tube conglutination reaction was positive with dilutions of the mother's serum up to 1:8. Tests of the infant's serum showed no Rh agglutinins or Rh blocking antibodies, but by means of the tube conglutination test Rh antibodies were readily demonstrable and clumping also occurred by the conglutination technic in mixtures of the infant's serum with her own cells.

*Course.*—The infant was given a transfusion of 85 cc. of group O, Rh-negative blood, following which the hemoglobin concentration rose to 100 per cent and the general condition of the infant seemed excellent. Two days later the hemoglobin concentration dropped abruptly to 50 per cent, and a second transfusion of 80 cc. of group O, Rh-negative blood was given. Following this, the hemoglobin concentration rose to 95 per cent, and thereafter it gradually declined and by the third week reached 60 per cent. At this time the infant's blood showed no Rh-positive red cells. The failure of Rh-positive blood to appear in the infant's circulation was readily explained by tests on the infant's serum for Rh antibodies. By the tube conglutination method, Rh antibodies of a titer of 5 units were still demonstrable at the end of the second week. By the end of the third week, the antibodies were still demonstrable, though the reactions seemed weaker. On the basis of these observations, it was obvious that the infant would need more blood. In fact, two additional transfusions had to be given before permanent recovery resulted. Incidentally, for these transfusions the packed washed red cells of the mother were used.

In this case, there was the usual history that the first child was normal and the second had congenital hemolytic disease. The question may arise why the first infant almost invariably escapes the disease unless the mother has had a previous transfusion of Rh-positive blood. If fetal blood enters the maternal circulation during the course of the pregnancy, it might be expected that in a certain proportion of cases

sensitization should advance sufficiently far before term to give rise to hemolytic disease in the infant. The probable answer is that no, or almost no, fetal blood gains access to the maternal circulation until term, at which time labor and delivery cause disturbances at the placental site. Evidence supporting this idea is the not infrequent rise in the maternal isoagglutinin titer occurring during the fortnight after delivery.[5]

The prognosis for future pregnancies in the present case is not quite so hopeless as in the other cases presented thus far. The father of the infant is Hr positive and therefore is likely to be heterozygous for the Rh factor (genotype $Rh_1rh$). This couple therefore probably has a 50 per cent chance of having an Rh-negative child who would not be susceptible to the maternal Rh antibodies.

The most interesting aspect of the case is the ease with which Rh antibodies were demonstrable in the infant's serum by the conglutination method.[6] This supports the contention that univalent antibodies (glutinins or blocking antibodies) are smaller molecules than bivalent antibodies (agglutinins) and thus the former can more readily traverse the placental barrier. When the infant's blood had been destroyed and replaced by Rh-negative blood, Rh glutinins were still present in substantial amounts. This indicates that there must have been a considerable excess of Rh antibodies in the infant's circulation. Yet the infant appeared normal at birth, and a few days passed before enough destruction of blood had occurred to attract the attention of the clinician. This supports the idea that X protein plays an important role in vivo as well as in vitro in the serologic reactions which bring

5. Hurst, J.; Taylor, H. C., and Wiener, A. S.: Individual Blood Differences in Relation to Pregnancy, with Special Reference to the Pathogenesis of Toxemia, Blood, to be published.

6. In this connection, we have found that the so-called "globulin technic" (Coombs, R. R. A.; Mourant, A. E., and Race, R. R.: Detection of Weak and "Incomplete" Rh Agglutinins, Lancet **2**:15 [July 7] 1945; A New Test for the Detection of Weak and "Incomplete" Rh Agglutinins, Brit. J. Exper. Path., **26**:255, 1945) can be adapted for use as a simple but delicate diagnostic test for congenital hemolytic disease. All that is necessary is to mix a drop of the infant's red cell suspension (washed three times with isotonic solution of sodium chloride) with a drop of suitably absorbed and diluted antihuman serum precipitin. If agglutination occurs, the infant is erythroblastotic; if there is no clumping, the diagnosis is excluded. Owing to lack of space, the test cannot be described in greater detail here.

Coating of the infant's red cells by univalent maternal antibodies may be demonstrated even more simply by the conglutination technic. Two drops of the infant's blood suspension are placed in a small tube and centrifuged. The supernatant saline solution is completely removed and replaced by normal compatible group A B plasma (or serum). The tube is shaken, placed in the water bath for half an hour and the reaction read.

about the destruction of the infant's red blood cells. As will be shown in the next case, in infants delivered by cesarean section the hemolytic process also starts soon after birth. This indicates that the profound physiologic changes which occur after birth probably bring about the formation of X protein by the combination of albumin, globulin and phospholipid (and, possibly, also fibrinogen) to form larger molecular aggregates.

CASE 6.—A married couple presented the following problem:

The first pregnancy (1941) resulted in the birth of a normal girl, living and well.

The second pregnancy (1943) ended with the birth of a full term infant who died on the third day. According to the parents, a blood donor was called but arrived after the baby had died.

The third pregnancy also terminated with the birth of a full term infant who died after twelve to fifteen hours.

The patient came for advice because she was pregnant again and was anxious to have a viable child. Results of blood tests on the patient, the husband and the living child were as follows:

| Blood of | Group and Subgroup | MN Type | Rh Type |
|---|---|---|---|
| Husband | O | MN | $Rh_1Rh_2$ |
| Patient | O | N | Negative |
| Daughter (4 years) | O | N | $Rh_1$ |

Examination of the patient's serum failed to reveal the presence of any anti-Rh agglutinins, but blocking antibodies of a titer of 1 unit were present. In addition, tube conglutination tests gave positive reactions and showed an Rh antibody titer of 5 units. In view of the presence of Rh blocking antibodies in the patient's serum, the prognosis for the present pregnancy was grave.

The suggestion was made that if the baby were delivered prematurely by cesarean section it might prove viable, because it then would be spared from too long exposure to the maternal Rh antibodies. Accordingly, four weeks before term, a cesarean operation was performed. Physical examination of the infant at birth showed no abnormality except jaundice. The infant's blood belonged to group O, type MN and type $Rh_1$, and the hemoglobin concentration was approximately 90 per cent. The blood smear showed that approximately 75 per cent of the nucleated cells were normoblasts and erythroblasts. The infant was given three transfusions of Rh-negative blood, totaling about 200 cc. in all. For the first transfusion, bank blood was used, and for the second and third the maternal washed red blood cells were used. The hemoglobin concentration was maintained, but, in spite of this, the blood smear continued to show numerous normoblasts and erythroblasts and the infant died after forty-eight hours. Autopsy showed kernicterus to be the cause of death.

This case again illustrates the more serious prognostic significance of the presence of blocking antibodies in the maternal serum as compared with that of Rh agglutinins. It also suggests that little is to be gained in such cases[7] by performing a cesarean operation in an

7. An exception is a case (case 3) previously reported by one of us (Wiener, A. S.; Wexler, I. B., and Gamrin, E. L.: Hemolytic Disease of the Fetus and New Born Infant, Am. J. Dis. Child. **68**:317 [Nov.] 1944).

attempt to protect the fetus from the maternal antibodies. This procedure merely exposes the mother to the additional hazard of a surgical operation and the infant to the dangers of prematurity without preventing the occurrence of hemolysis, which, if it has not already taken place, will start promptly after delivery. This tends to support our view that the profound physiologic changes which occur after birth, in particular, dehydration and change in temperature, may cause the formation of X protein in the blood of the infant, thus precipitating the occurence of hemolysis.

It should be mentioned here that the grave prognosis anticipated in this case led us to be somewhat more zealous in our transfusion treatment than is our usual custom. The original plan was to perform a complete exsanguination transfusion, but this plan was not carried out because of the anticipated technical difficulties. Instead, we decided to give somewhat larger doses of blood than the ordinary, but our efforts were of no avail. As a result of this experience, we have resumed our regular practice of calculating the amount of blood to be given to the infant on the basis of its hemoglobin concentration, because there is some danger in giving too much blood.

First, our practice is to give approximately 10 cc. per pound (454 Gm.) of body weight at one time. Considering that the average infant of 7½ pounds (3,400 Gm.) has a blood volume of approximately 250 cc., a transfusion of 75 cc. of fresh Rh-negative blood should be sufficient to guarantee that the infant's hemoglobin concentration will not drop below 30 per cent. Two such transfusions would be certain to maintain the hemoglobin concentration above 60 per cent; a third transfusion would guarantee a hemoglobin concentration of 90 per cent and so on. Second, one must bear in mind that all a transfusion can accomplish is to replace the hemolyzed blood of the infant. That is, blood transfusion is lifesaving only in cases in which death would occur because of anemia and is of no avail in the presence of such lethal complications as kernicterus, severe hepatic and renal damage and hemorrhage into the brain and lungs. Therefore, there is little or nothing to be gained by giving the infant transfusions before anemia has actually developed. Our usual practice is not to give these infants transfusions before the hemoglobin concentration drops below 80 per cent. When the hemoglobin concentration is between 70 and 80 per cent, a single transfusion of 75 cc. of blood should be given, and the transfusion should not be repeated until and unless the hemoglobin concentration again drops below 80 per cent. If the infant's hemoglobin concentration is as low as 50 per cent when first seen, an immediate transfusion of 75 cc. should be given, and the transfusion should be repeated within eight to twenty-four hours. A simpler procedure in such cases is to give a single transfusion of the packed red cells from

150 cc. of Rh-negative blood. This is most readily done by drawing the blood from the mother and washing and packing her red cells, a procedure which obviates the need for any grouping or Rh tests. When the infant's hemoglobin concentration is extremely low, for example, as low as 20 to 30 per cent, an initial transfusion of as much as 150 cc. of blood at one time is entirely safe and may be lifesaving.[7] Once the initial one or two transfusions have been given, the patient is out of danger. The worst that can happen is that a severe anemia may develop in the patient during the course of weeks, from which spontaneous recovery would be the rule. However, for the well-being of the infant, it is best to maintain the hemoglobin level between 60 and 80 per cent. We consider another transfusion to be indicated when the hemoglobin level drops below 60 per cent, particularly if the blood smears show no reticulocytes and the differential agglutination tests show no Rh-positive red blood cells. Many of the infants require an additional one or two transfusions by the time they are 1 month old. Only rarely have we had to give as many as five transfusions. By the time the infants are 3 months old, they have usually recovered fully and have replaced most, if not all, of the transfused red cells by their own Rh-positive cells.

A physician recently informed us of a case in which an infant was given as many as eight transfusions of packed Rh-negative blood cells over a two month period. The infant died, and before death the blood had a hematocrit reading of 66 per cent. In view of the improper management of the transfusions there seems little doubt that this patient had been given too much blood.

CASE 7.—We were requested to see a 5 day old boy with the following history: He was born on Jan. 10, 1945, and jaundice was noticed on the following day. On the fifth day, the jaundice was deeper and the blood count showed the patient's hemoglobin concentration to be 60 per cent, with 2,900,000 red blood cells per cubic millimeter and 5 per cent normoblasts on smear of the blood. The patient was the eighth child born to his mother. All her previous pregnancies had terminated with normal full term infants, all alive and well, except the first, who had died as a result of an accident.

Results of grouping and Rh tests of the patient, his parents and the siblings were as follows:

| Blood of | Group and Subgroup | MN Type | Rh Type | Hr Reaction |
|---|---|---|---|---|
| Father | O | M | $Rh_1$ | Negative |
| Mother | O | M | Negative | Positive |
| Brother (born 1931) | O | M | $Rh_1$ | Positive |
| Sister (born 1933) | O | M | $Rh_1$ | Positive |
| Sister (born 1938) | O | M | $Rh_1$ | Positive |
| Sister (born 1939) | O | M | $Rh_1$ | Positive |
| Sister (born 1941) | O | M | $Rh_1$ | Positive |
| Brother (born 1942) | O | M | $Rh_1$ | Positive |
| Sister (born 1943) | O | M | $Rh_1$ | Positive |
| Patient | O | M | $Rh_1$ | Positive |

Tests on the maternal serum showed no anti-Rh agglutinins, but a weak blocking reaction was obtained, while the reaction to the tube conglutination test

was positive to a titer of 16 units. Tests of the infant's serum by the conglutination method also showed the presence of Rh antibodies of low titer (1 unit), and autoagglutination of the patient's red cells by his own plasma was also readily demonstrable. These observations, therefore, established the diagnosis of hemolytic disease of the newborn.

The infant was treated by two transfusions of 90 cc. each of group O, Rh-negative blood, and when discharged a week later he had a hemoglobin concentration of 85 per cent. The patient was not seen again until he was 5 weeks old, at which time the hemoglobin level had dropped to 45 per cent. A transfusion of the packed washed cells of the mother's blood was given, and the hemoglobin level rose to 72 per cent, the rise this time being sustained. The patient was last seen on August 29, when he was entirely normal.

The unusual feature of this case is the large number of pregnancies with Rh-positive fetuses before the mother was sufficiently sensitized to have an infant with congenital hemolytic disease. Had the family been smaller, there would have been no indication that the patient's mother was capable of being sensitized to the Rh factor. Thus, one condition affecting the incidence of congenital hemolytic disease in a population is the average size of the family.

This family illustrates once more the value of the Hr reaction as a presumptive test for homozygosity or heterozygosity. The father belongs to type $Rh_1$ Hr negative. As was expected, under the assumption that he therefore belongs to genotype $Rh_1Rh_1$, every one of the 7 children tested proved to be type $Rh_1$, Hr positive.

CASE 8.—A patient presented the following problem:

Her first pregnancy (1941) terminated with an incomplete abortion, and dilation and curettage were performed.

Her second pregnancy (1942) ended with the birth of a normal girl who is living and well.

Her third pregnancy terminated on July 27, 1944 with a boy who appeared entirely normal at birth. The following day, jaundice was noticed, but the hemoglobin concentration was 120 per cent with a red blood cell count of 5,800,000. The following day the jaundice deepened, but the hemoglobin level remained at 120 per cent. On the evening of this day, the infant took his feeding poorly and vomited. A few hours later, he bled from the nose and mouth and died shortly afterward. The most important observation at autopsy were hemorrhage into the lung and islands of hemopoiesis in the liver and spleen. The patient was informed that the infant had died of congenital hemolytic disease, and she wished to know whether anything could be done to prevent the recurrence of the condition in future pregnancies.

Grouping and Rh tests on the patient, her husband and their surviving child gave the following results:

| Blood of | Group and Subgroup | MN Type | Rh Type | Hr Reaction |
|---|---|---|---|---|
| Husband | O | M | $Rh_0$ | Positive |
| Wife (patient) | $A_1$ | M | Negative | Positive |
| Daughter (3 years) | $A_1$ | M | $Rh_0$ | Positive |

The patient's serum contained Rh agglutinins of high titer and of specificity $Rh_0$". (The anti-Rh" agglutinins had a titer of 256, and the anti-$Rh_0$ agglutinins

had a titer of 128.) These observations therefore established the diagnosis of congenital hemolytic disease as the cause of death of the infant.

This case had several unique features. First, the clinical manifestations of the disease in the infant were unusual, the infant dying with hemorrhagic symptoms rather than from hemolysis of the red cells. No transfusion was attempted because of the high hemoglobin concentration and because in our past experience with this type of manifestation transfusion therapy has proved to be of no avail.[8] Perhaps exsanguination transfusion would have forestalled the occurrence of hemorrhage, but this is a formidable procedure to carry out. The second remarkable feature is the unusual specificity of the Rh antibodies in the maternal serum and their high titer.

In an attempt to reduce the high antibody titer, a series of exchange transfusions were given starting Jan. 14, 1945, in which 500 cc. of the patient's blood was withdrawn and replaced with 500 cc. of blood from normal male group A, Rh-negative professional donors. For a short time, this procedure seemed to have reduced the antibody titer. When after the thirteenth exchange transfusion, in September 1945, more than one year after the birth of the erythroblastotic infant, the titer of Rh agglutinin, instead of falling, resumed its original level, it was evident that this line of treatment was futile, and the transfusions were discontinued. The patient was also given a course of subcutaneous injections of typhoid-paratyphoid vaccine and pertussis vaccine, without apparent effect. With regard to the injection of vaccines, this is evidently useless once sensitivity has developed. The application of the principle of competition of antigens is much more hopeful as a prophylactic than as a cure.

With regard to the prognosis for future pregnancies, it was important to determine the homozygosity or heterozygosity of the husband. Theoretically, this might be done with the aid of the anti-Hr″ serum recently described by Mourant,[9] but this type of serum is extremely rare and was not available to us. Therefore, grouping and Rh tests were carried out on the husband's parents with the following results:

| Blood of | Group and Subgroup | MN Type | Rh Type | Hr Reaction |
|---|---|---|---|---|
| Husband's father..... | O | MN | $Rh_1Rh_2$ | Positive |
| Husband's mother..... | O | M | $Rh_1Rh_2$ | Positive |

These results indicate that the husband is homozygous for the Rh factor (either genotype $Rh_2Rh_2$ or $Rh_2Rh''$); hence every future child must be Rh positive and have hemolytic disease. Shortly after these studies were completed, the patient became pregnant, and a therapeutic abortion was performed.

Case 9.—The patient was a girl 3 weeks of age, who was referred to us for blood studies, with the following history: The patient had been born three

8. In our experience when any erythroblastotic infant has a high hemoglobin concentration, while this may mean that the process is mild, more often the outcome is lethal. Therefore, we feel much more comfortable with patients in whom anemia of severe degree develops, because they usually do well with transfusion therapy.

9. Mourant, A. E.: A New Rhesus Antibody, Nature, London **155**:542 (May 5) 1945. Wiener, A. S.: Theory and Nomenclature of the Hr Blood Factors, Science **102**:479 (Nov. 9) 1945.

weeks prematurely, and jaundice was noticed shortly after birth. Nevertheless, the infant was discharged from the hospital at the same time as her mother. When seen by us, the infant appeared very pale, and her hemoglobin concentration proved to be only 50 per cent. The blood smear showed that about half the red cells were reticulocytes, and there were 2 normoblasts per 100 white cells. In view of these results, a diagnosis of congenital hemolytic disease was entertained.

The patient's mother had had only one previous child, who was alive and well. Results of grouping and Rh tests of the family were as follows:

| Blood of | Group and Subgroup | MN Type | Rh Type | Hr Reaction |
|---|---|---|---|---|
| Father | O | N | $Rh_1$ | Negative |
| Mother | $A_1$ | MN | Negative | Positive |
| Sister (4 years) | O | MN | $Rh_1$ | Positive |
| Patient | $A_1$ | MN | $Rh_1$ | Positive |

Examination of the mother's serum showed anti-Rh′ agglutinins, with a titer of 16 units and anti-$Rh_0$ blocking antibodies with a titer of 4 units.

*Course.*—The patient was then referred to the hospital and treated with transfusions of bank blood as follows:

March 15, hemoglobin concentration, 50 per cent.
March 16, 70 cc. of group A, Rh-negative bank blood.
March 17, 50 cc. of group A, Rh-negative bank blood.
March 18, 55 cc. of group A, Rh-negative bank blood.
March 20, hemoglobin concentration, 58 per cent.
March 21, 65 cc. of group A, Rh-negative bank blood.
March 23, 65 cc. of group A, Rh-negative bank blood.
March 26, hemoglobin concentration, 60 per cent.
March 27, 75 cc. of group A, Rh-negative bank blood.
March 29, 70 cc. of group A, Rh-negative bank blood.

On April 3 and April 6, the hemoglobin concentration was 88 per cent, and the patient was discharged from the hospital.

By April 28, the hemoglobin concentration had dropped to 65 per cent, and half of the red cells were still Rh negative. On May 21, the hemoglobin concentration was 70 per cent, and at this time only one tenth of the red cells were Rh negative. On June 2, the hemoglobin concentration was 68 per cent, and all the red cells were Rh positive. The infant was seen again on August 15, at which time she appeared to be entirely well clinically.

This case has two unusual features. First, the onset of the disease was so insidious that the diagnosis was entirely missed at the hospital where the patient was born and was not made until the infant was referred to us for a blood count when it was 3 weeks old. With this prolonged delay before the institution of treatment, it is fortunate that the infant survived. The second unusual feature is the large amount of blood required before permanent recovery resulted. This we attribute to the use of bank blood, which is contrary to our usual practice. We prefer to use fresh blood because if poorly preserved bank blood is transfused the red cells may not survive long in the patient's circulation. Accordingly, the use of bank blood for treating infants with congenital hemolytic disease is wasteful.

CASE 10.—The patient was a boy, who was born May 7, 1945. He was observed carefully because the mother gave the following obstetric history:

The first pregnancy resulted in the birth of a normal girl who is alive and well.

The second pregnancy, in 1936, terminated with the birth of an infant who had congenital hemolytic disease and died when 4 days old.

The outcome of the third pregnancy, in 1938, was a girl who had congenital hemolytic disease and who recovered after a single transfusion.

Results of grouping and Rh tests on the patient, his parents and siblings were as follows:

| Blood of | Group and Subgroup | MN Type | Rh Type | Hr Reaction |
|---|---|---|---|---|
| Father | O | MN | $Rh_1Rh_2$ | Positive |
| Mother | $A_1B$ | MN | Negative | Positive |
| Sister (14 years) | B | MN | $Rh_1$ | Positive |
| Sister (7 years) | B | MN | $Rh_2$ | Positive |
| Patient | B | MN | $Rh_2$ | Positive |

Tests on maternal serum showed no Rh agglutinins or blocking antibodies, and only very weak Rh antibodies were demonstrable in the conglutination test. There seemed no doubt that congenital hemolytic disease would develop in the infant, but, in view of the low antibody titer of the mother's serum, it was anticipated that the hemolysis would be mild.

*Course.*—The infant's hemoglobin concentration at birth was 120 per cent. It dropped gradually so that by the fourth day it had reached 88 per cent, and at this time he appeared definitely jaundiced. He was given a transfusion of 75 cc. of group O, Rh-negative blood. Following this, the hemoglobin level rose to 94 per cent and then dropped back to 90 per cent, a level at which it remained until the patient was discharged a week later. The infant was not seen again until June 2, when he looked pale but was well otherwise. At this time, a blood count showed the hemoglobin concentration to be only 50 per cent and a blood smear showed numerous polychromatic and nucleated red cells. The infant was given a transfusion of the packed washed cells from 150 cc. of the mother's blood. The hemoglobin then rose to 85 per cent, and the improvement this time was maintained.

The unusual feature of this case is that the disease was mild, despite the fact that 2 preceding siblings had had congenital hemolytic disease. Apparently some Rh-negative women are readily sensitized to the Rh factor but are nevertheless capable of developing only a low degree of sensitivity. Probably if the infant's mother were given a transfusion of Rh-positive blood, she would have only a mild hemolytic reaction and the bulk of the transfused red cells would survive for a long time in her circulation. In fact, we have seen a number of instances of mild intragroup transfusion hemolysis which give this type of picture. After the transfusion, such patients are temporarily desensitized, and no Rh antibodies can be demonstrated in their serum for a considerable length of time. This plus the survival of the bulk of the donor's red cells makes the diagnostic problem difficult in such cases.

Considering the Rh type of the patient's father (type $Rh_1Rh_2$), it seems inevitable that all the future children in this family will have

congenital hemolytic disease. However, most likely such infants would all be born alive and should survive with proper transfusion therapy.

CASE 11.—This patient and her husband were referred to us by Dr. S. A. Wolfe and offered the following problem:

The first pregnancy (1935) resulted in the birth of a full term boy, now living and well.

The second pregnancy (1943) terminated with a seven-month stillbirth.

The outcome of the third pregnancy (1944) was a full term girl who lived only two days.

The patient was now in the fourth month of her fourth pregnancy, and it was easy to understand the concern of the patient and her physician in view of her obstetric history, which strongly suggested the diagnosis of congenital hemolytic disease.

The blood tests gave the following results:

| Blood of | Group and Subgroup | MN Type | Rh Type |
|---|---|---|---|
| Husband | $A_2$ | MN | $Rh_1Rh_2$ |
| Patient (wife) | $A_2$ | N | Negative |
| Son (9 years) | $A_2$ | MN | $Rh_2$ |

These observations appeared to support the diagnosis of congenital hemolytic disease except that the patient's serum contained no detectable Rh antibodies. When repeated examination throughout pregnancy still failed to reveal the presence of Rh antibodies either on the agglutination or the conglutination tests, it became evident that the patient was not sensitized to the Rh factor. We then became convinced that the 2 infants that had been lost did not die from congenital hemolytic disease, and we even offered a good prognosis for the expected infant.

Toward the end of the ninth month of pregnancy, the patient remarked that she no longer felt life, and the obstetrician at the same time detected the presence of glucose in her urine. A hematologic examination showed the blood sugar to be 250 mg. per hundred cubic centimeters. A few days later labor was induced, and the patient delivered a macerated fetus. The history was then elicited that diabetes developed in the patient's mother after she had given birth to several normal children, and that then she had a number of stillbirths.

This case serves to emphasize the fact that congenital hemolytic disease and syphilis are not the only causes of repeated stillbirths and neonatal deaths. Other investigators[10] have already remarked the similarity between the clinical behavior of infants with mothers having latent diabetes and infants with congenital hemolytic disease. The case we have described serves to emphasize the value of the conglutination test for the detection of or for ruling out Rh sensitization.

## SUMMARY AND CONCLUSIONS

1. The Hr test is a valuable aid in determining the homozygosity or heterozygosity of type $Rh_1$. When the Hr test is negative, the person is homozygous (either genotype $Rh_1Rh_1$ or genotype $Rh_1Rh'$), while

10. Miller, H. C.; Johnson, R. D., and Durlacher, S. H.: Comparison of Newborn Infants with Erythroblastosis Fetalis with Those Born to Diabetic Mothers, J. Pediat. **24**:603 (June) 1944.

if the Hr test is positive, he is almost surely heterozygous. If a man is homozygous for the Rh factor and his wife's serum contains Rh blocking antibodies, the prognosis for future pregnancies is virtually hopeless.

2. In the presence of Rh sensitization, transfusions of plasma should be given instead of transfusions of blood unless Rh-negative donors are available.

3. Even a small intramuscular injection of Rh-positive blood may be sufficient to sensitize an Rh-negative woman and in that way to prevent her from having viable infants.

4. The injection of a potent antigen may prevent a person from becoming sensitized to a weaker antigen to which he or she is exposed simultaneously. For example, the injection of typhoid or pertussis vaccine during pregnancy may be worth while in the case of Rh-negative patients with sisters who have had erythroblastotic infants. Once sensitization has developed, however, counterimmunization does not appear to affect the degree of sensitization.

5. That univalent antibodies (blockers) are more important than bivalent antibodies (agglutinins) in the pathogenesis of congenital hemolytic disease is proved by the ease with which the former can be demonstrated in the serum of erythroblastotic infants in the absence of agglutinins. This accounts for the lack of correlation between the isoagglutinin titer of the maternal serum and the severity of the hemolytic process in the infant.

6. In the transfusion therapy of congenital hemolytic disease, the washed red cells of the mother can always be used, even though the mother belongs to a blood group incompatible with that of the child. The reason is that every infant's antibodies during the neonatal period were passively acquired from the mother by placental transfer; hence a newborn infant's serum never contains antibodies capable of reacting with the maternal red cells.

7. Early cesarean section is often ineffectual in the prevention of congenital hemolytic disease, because the disease may be initiated by the birth of the infant. According to our theory, the profound physiologic changes occurring after birth cause the formation of X protein in the infant's plasma and thus favor the onset of hemolysis. Besides, cesarean section subjects the mother to the additional hazards of an operation and the infant to the hazards of prematurity.

8. The presence of high hemoglobin concentration in an infant with hemolytic disease may merely mean that the disease process is mild, but frequently in such cases kernicterus or hemorrhagic manifestations develop and the infants die. In any event, there is nothing to be gained by prophylactic transfusions before the hemoglobin drops

below 80 per cent, because the only effect of transfusion therapy is to correct the anemia and the only infants benefited are those who would otherwise die from anemia. In any case, transfusion of too much blood is to be avoided because this is dangerous.

9. Women differ in the ease with which they can be sensitized to the Rh factor; while some require only one or two pregnancies or transfusions, occasionally sensitization does not develop until there have been as many as seven to ten or more pregnancies. Once sensitization develops, it appears to be permanent, though patients differ in the degree of sensitization. Thus, some patients may have repeated stillbirths while others have viable infants who recover after transfusion therapy.

10. An unusual case is reported of a woman in whom high titers of anti-$Rh_0$ and anti-Rh″ agglutinins developed after she had given birth to an infant type $Rh_2$ who died of hemolytic disease. The titer of the antibodies showed hardly any change after twelve exchange transfusions of blood from normal Rh-negative male donors. The husband was shown to be homozygous for the Rh factor; therefore when the patient became pregnant a therapeutic abortion was performed.

11. For giving transfusions to infants with hemolytic disease, fresh blood when available is preferable to bank blood. Improperly stored blood breaks down quickly in the infant's circulation, and many more transfusions may be necessary.

12. Mothers with latent diabetes may have an obstetric history clinically indistinguishable from that of mothers whose infants have erythroblastosis fetalis. In 1 such case the difficulty of diagnosis was increased by the fact that the patient was Rh negative and the husband Rh positive. In such instances, tests for Rh antibodies in the maternal serum by the conglutination as well as the agglutination method are reliable aids in the differential diagnosis.

# SUCKING RESPONSE OF NEWLY BORN BABIES AT BREAST

## A Study of Fifty Cases

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IN order to learn more about the response of the normal baby to the breast and in order to interest more mothers in the breast feeding of their babies, observations were made on the sucking response of 50 newly born babies at the breast. Sucking, aided by nuzzling and lip reflexes, is a determining factor in successful breast feeding. Stroking the lip or cheek arouses these reflexes, causing the baby to turn his head toward the source of stimulation. A satisfactory response is stimulated further if the breast of the mother has a nipple that can be seized and drawn out and if the mother cooperates in presenting the breast to the baby.

The feeding response of 50 consecutive full term, normal babies was studied intensively. The infants were observed at the breast three to five times daily during their stay of nine or ten days in the hospital. One baby or not more than 2 was observed at a time. No selection of the babies was made except that those delivered by cesarean section were not included, since they are not sent for breast feeding until the third day after delivery.

Six to fourteen hours after delivery, each baby was sent to his mother for the first time, and thereafter it was sent approximately every four hours throughout the day and night. The mother was advised to find a comfortable position before offering the nipple, and, since the first three or four days are considered to be a practice period for both mother and baby, she was advised not to let the baby suck longer than two to four minutes at each breast. After the milk had "come in," this time was extended to seven to fifteen minutes on each side. If the mother felt that she and the baby adjusted more easily by using one breast instead of two at each nursing, this change was made. After breast feeding during the three or four day practice period, the baby was given by bottle as much of a 10 per cent solution of dextrose in water as he cared to take. No supplementary formulas of milk were given to any of these babies unless the mother's milk supply had proved inadequate at the end of the first week. If the baby was sleepy when it was time for breast feeding, he was awakened

From the Rochester Child Health Project.

by being placed in a sitting position and by pats on the back. No vigorous attempts were made to coax, spank or prod the baby into feeding.

Each baby and mother had a natural approach to the nursing problem, and the initial responses seemed to remain constant from one feeding to the next during the period of observation. The rate of sucking was faster at the beginning than toward the end of the feeding period, but it increased temporarily when the second breast was offered. Most of the babies expressed their satiety by falling asleep at the breast.

The responses of the babies were of three types: vigorous, average and poor. According to our estimate, the sucking response of 10 was vigorous, of 38 average and of 2 poor.

The vigorous ones would take hold of the nipple almost immediately after it was offered and suck actively or even greedily. Delay or difficulty in sucking occurred in 2 instances. One of the babies had trouble with mucus in his throat the second time he was in his mother's room. After he had cleared this out, he nursed well. The other baby appeared to be wide awake the first time he visited his mother, closed his mouth over the nipple and then turned his head away. He repeated this action for several minutes before he began to suck.

Most of the babies in the average group would grasp the nipple as soon as they were placed at their mothers' breasts. They tended to fall asleep soon and let go of the nipple but could easily be started sucking again by a gentle pat. Some would push the nipple out of their mouths or hold it for a while before beginning to suck. A few preferred to look around and "root" or cry before beginning. Three babies in this group made no attempt to suck either the first or the second time at the breast. One of these had difficulty clearing out mucus at the first two feedings. The other 2 were sleepy at their first feedings, but after the second feeding they did well. They were 6 and 12 hours old respectively at the time of their first feedings. Barbiturates had been given to their mothers during labor, but the amount was no larger than that usually given.

The 2 babies who gave a poor response to the breast had been delivered spontaneously after uneventful gestations. The primiparous mother was in labor for four and a half hours and the multiparous mother for ten hours. Both babies cried immediately after birth. The smaller of the infants weighed 6 pounds 9 ounces (2,975 Gm.). Physical examinations at birth and during the stay in the hospital revealed that both of these babies were normal.

The first of these infants appeared sleepy and would either cry or suddenly fall asleep at the breast. He made no attempt to suck until the end of the third day, and even then the response seemed to be fleeting. When given the bottle of dextrose solution he made feeble

attempts at sucking but would swallow any fluid that dropped into his mouth. In the nursery he slept all the time, and it was necessary to rouse him at each feeding time. At the end of a week he was given an artificial formula because his mother had an inadequate supply of milk even when the breasts were pumped. His weight at dismissal, on the tenth day, was 4.5 ounces (130 Gm.) more than at birth; perhaps this weight was due in part to his lack of activity.

The other baby in this group would make a few sucking movements, then let go of the nipple and "root," cry or fall asleep. This behavior continued throughout his nine days' stay in the hospital. According to DeLee [1] and others,[2] this behavior is similar to that seen when there is an insufficient supply of milk. At the time of dismissal the baby was obtaining an adequate supply of milk from his mother; he weighed 1 ounce (28 Gm.) less than at birth.

In this series of cases, 4 per cent of the babies had persistent difficulty in nursing at the breast during the neonatal period. According to records of the newly born babies made in the past eighteen months, 9 per cent were classified as having a poor nursing response in the beginning. This apparent discrepancy between the two sets of observations may be accounted for by the difference in methods of observation. In the larger group the opinions of mothers and of nurses had been accepted without question, while in this smaller group, the observations were made by one trained observer. The basis of classification used by one person would be less variable and more definite than that used by several nurses and mothers.

Statements can be found in the literature ranging from opinions that all newly born babies nurse well to observations that 40 per cent have difficulty in nursing. Blanton [3] had the obstetrician stick his gloved finger into the baby's mouth during the first hour of life. Judged by this method, no baby refused to suck. Sedgwick and Cole [4] found that many babies placed at the breast for the first time grasped the nipple at once and nursed with strength and vigor, whereas others were slow to grasp it and then gave only a few tugs before letting go. The infants seemed to repeat this procedure at each feeding. Some were found to be sleepy and needed to be roused and kept awake.

1. DeLee, J. B.: The Principles and Practice of Obstetrics, ed. 5, Philadelphia, W. B. Saunders Company, 1928.

2. Gunther, M.: Lactation in Women, Canad. M. A. J. **47**:410-414, 1942. Richardson, F. H.: The Nursing Mother: A Study in Lactation, New York State J. Med. **22**:161-165, 1922.

3. Blanton, M. G.: The Behavior of the Human Infant During the First Thirty Days of Life, Psychol. Rev. **24**:456-483, 1917.

4. Sedgwick, J. P., and Cole, W. C. C.: Breast Feeding and Nutrition, in Abt I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 2, chap. 22, pp. 583-621.

Figures were not given on the number in each group. Ribble [5] found that at least 40 per cent of the 600 infants studied could not suck vigorously enough to get their own nourishment until they had been prompted and assisted repeatedly. This is several times the percentage of babies encountered in this study who had any difficulty in nursing in the neonatal period.

## SUMMARY AND CONCLUSIONS

According to this study, the sucking response of 20 per cent of the 50 newly born babies at the breast was vigorous, of 76 per cent average and of 4 per cent poor. The vigorous ones would grasp the nipple and suck eagerly; those in the average group tended to fall asleep while sucking but could be roused easily, whereas those who gave a poor response made only short feeble attempts at sucking. Under conditions in which supplementary milk formulas are not given until the mother's supply of milk has been proved inadequate and in which the mothers are given adequate instructions on how to cooperate with their babies, 96 per cent of the infants suck well at the breast.

From this study it may be concluded that the average early response of newly born babies to the breast is not a greedy one but is characterized more by dallying and repetitious trials at nursing. This behavior should be met with patience and with calm attempts to allow the baby to learn the gratification he can get from nursing rather than with vigorous unpleasant stimulation.

5. Ribble, M. A.: The Rights of Infants: Early Psychological Needs and Their Satisfaction, New York, Columbia University Press, 1943.

# KAPOSI'S VARICELLIFORM ERUPTION

## Studies on Etiology

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KAPOSI'S varicelliform eruption was first described in 1887,[1] as a rare and dramatic complication of infantile eczema. Since the original description, other, more descriptive, names have been given to this condition, such as acute vacciniform pustulosis or acute varioliform pustulosis.

It occurs in persons who have been suffering from some dermatosis, usually eczema, and, more commonly, infantile eczema. It is characterized by a sudden onset of high fever followed in a few hours by inflammation and edema of the skin and the appearance of many of the characteristic umbilicated pustules. These pustules are 2 to 3 mm. in diameter, have an erythematous base and usually contain pus from the onset. The lesions are invariably most numerous on the previously affected areas of the skin, which in infants with eczema are usually the face and the scalp, though a few pustules often occur on the extremities or the buttocks. Associated lymphadenopathy of the regional nodes is the rule. The fever usually persists for from two to three weeks, during which time new crops of pustules may appear. The outcome is most often favorable, though several fatal cases have been reported. Slight atrophic scarring of the skin occurs in most cases.

A review of the literature on Kaposi's varicelliform eruption reveals that its cause is still not established. Juliusberg,[2] in 1898, was the first to suggest that a secondary infection of the underlying eczema with Staphylococcus aureus was responsible for the development of the characteristic umbilicated pustules and clinical course. Since then, many others, Baar,[3] Freund,[4] Freud,[5] Streitmann,[6] Höffken,[7]

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1. Kaposi, M.: Pathologie und Therapie der Hautkrankheiten, Vienna, Urban & Schwarzenberg, 1887, p. 483.

2. Juliusberg, F.: Ueber Pustulosis acuta varioliformis, Arch. f. Dermat. u. Syph. **46**:21, 1898.

3. Baar, H.: Ein Fall von Pustulosis vacciniformis, Wien. med. Wchnschr. **81**:1157, 1931.

*(Footnotes continued on next page)*

Goyert,[8] and Brain and Lewis,[9] have reported finding staphylococci on culture of material from the lesions, while, of these, only Freud, Streitmann, Höffken and Goyert appear to have considered this organism to be the etiologic agent. Streitmann [6] and Goyert [8] pointed out that there are other known conditions caused by staphylococci which result in umbilicated vesicles, such as ecthyma vacciniforme. Obviously, however, the mere presence of staphylococci in lesions of the skin and the knowledge that these organisms may produce similar lesions are insufficient evidence to prove that they are the cause. H. Freund's theory that the disease is the result of infection with a much attenuated vaccinia virus plus Staph. aureus is one which deserves attention, as viruses are known to prepare the ground for bacterial infection.

The possible relationship of Kaposi's varicelliform eruption to varicella and variola has been considered since the condition was first described. However, the general systemic symptoms are too severe for varicella and not severe enough for variola with a corresponding amount of eruption. These observations and the absence of secondary cases of either disease in spite of many known susceptible contacts have rightfully prevented serious consideration of these viruses as the etiologic agents.

One is struck by the marked similarity of the pustule of Kaposi's varicelliform eruption to the pustule of vaccinia, both as it appears locally and as it appears in the generalized varieties. Jadassohn,[10] Ellis,[11] Tedder,[12] and Graves and Dowman [13] expressed the opinion that eczema

4. Freund, H.: Zur Aetiologie der Pustulosis vacciniformis acuta (Kaposi-Juliusberg), Dermat. Wchnschr. **98**:52, 1934; abstracted, Yearbook of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1934.

5. Freud, P.: Ueber Pustulosis vacciniformis acuta, Monatschr f. Kinderh. **51**:28, 1931; Ein Fall von Pustulosis Vacciniformis acuta, Wien. med. Wchnschr. **81**:1157, 1931.

6. Streitmann, B.: Ueber varioliforme Pyodermien, Arch. f. Dermat. u. Syph. **178**:99, 1938.

7. Höffken, K. H.: Ein Beitrag zur Pustulosis vacciniformis acuta, Kinderärztl. Praxis **9**:3, 1938.

8. Goyert, K.: Ein Beitrag zur Pustulosis vacciniformis acuta, Dermat. Wchnschr. **108**:478, 1939.

9. Brain, R. T., and Lewis, B.: The Investigation of Virus Diseases of the Skin, with a Report of a Case of Kaposi's Varicelliform Eruption, Brit. J. Dermat. **49**:551, 1939.

10. Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 6, p. 200.

11. Ellis, F. A.: Eczema Vaccinatum: Its Relation to Generalized Vaccinia, J. A. M. A. **104**:1891 (May 25) 1935.

12. Tedder, J. W.: Eczema Vaccinatum, Arch. Dermat. & Syph. **34**:1008 (Dec.) 1936.

*(Footnotes continued on next page)*

vaccinatum and Kaposi's varicelliform eruption are one and the same disease. They pointed out that in the past the differentiation in many cases was based on the fact that the authors were unable to elicit a history of exposure to vaccine virus and that some of the patients with Kaposi's varicelliform eruption had been previously successfully vaccinated. The lack of history of exposure, is, of course, purely negative evidence and not conclusive. Furthermore, Ellis [14] and Tedder [12] emphasize that eczema vaccinatum also is known to occur after successful vaccination or even in second attacks.

Most of the recent writers [15] who have concerned themselves with etiology seem to feel that vaccinia virus is responsible, at least in part, for this clinical picture. In support of this view, Freund,[4] in addition to finding staphylococci in the lesions, was able to demonstrate the presence of definite Guarnieri's bodies in the cornea of a rabbit inoculated with the fresh contents of a pustule from his patient with Kaposi's varicelliform eruption. Since he was able to vaccinate his patient successfully eight weeks after recovery, he postulated that the vaccinia virus which he isolated was so attenuated as to be unable to produce immunity in the patient.

Against the general acceptance of the theory that vaccinia virus is the etiologic agent, it should be noted that while Freud,[5] Höffken,[7] Goyert [8] and Brain and Lewis [9] have been able to produce a keratitis on inoculation of the scarified rabbit's cornea with material from patients with Kaposi's varicelliform eruption, none of them has been able to demonstrate the presence of Guarnieri's bodies. Serum of the rabbit inoculated by Brain and Lewis [9] showed no agglutinins or precipitins and no neutralizing power against vaccinia virus. Some writers, including Kooij,[16] Streitmann [6] and Bettley,[17] obtained negative results on inoculating the scarified rabbit's cornea with virus material from their patients.

Vesicular cutaneous lesions are also produced by the virus of herpes simplex. Although this virus has not been seriously considered as the etiologic agent, a search of the literature reveals some evidence on this point. Streitmann,[6] Höffken [7] and Freud [5] stated that they were

13. Graves, G., and Dowman, C.: Accidental Smallpox Vaccination and Eczema Vaccinatum, New York State J. Med. **37**:1833, 1937.

14. Ellis, F. A.: Kaposi's Varicelliform Eruption, Brit. J. Dermat. **48**:524, 1936.

15. Freud.[5] Jadassohn.[10] Ellis.[11] Tedder.[12] Graves and Dowman.[13]

16. Kooij, R.: Pustulosis varioliformis s. vacciniformis acuta, Nederl. tijdschr. v. geneesk. **81**:571, 1937.

17. Bettley, F. R.: Kaposi's Varicelliform Eruption: Some Experimental Findings, Brit. J. Dermat. **52**:222, 1940.

unable to find herpetic inclusion bodies in the cornea of the rabbit in which keratitis developed following inoculation with virus from their patients with Kaposi's varicelliform eruption. However, there is great difficulty in finding these inclusion bodies, even when they are known to be present.

In this connection, an interesting case of vacciniform blepharitis was reported by Andervont and Friedenwald,[18] in which they definitely established an atypical herpes virus as the cause. The importance of this in relation to the study of the present case is that the excellent color plate of their patient shows lesions identical in character with Kaposi's varicelliform eruption.

## REPORT OF A CASE

C. P., a 6 month old Negro boy, was admitted to the Children's Hospital of Philadelphia[19] on Dec. 23, 1941. The important items in his past history are that he had been under treatment at another hospital for about two months because of a mild eczema of the scalp and face. He had had no previous immunizations. About three weeks prior to the onset of the illness, his elder brother was vaccinated against smallpox, and nine days later a pustule appeared at the site of vaccination, which developed as a characteristic nonimmune "take." The mother stated that about one week prior to admission, the baby's skin had suddenly become much worse and that many "blisters" had appeared, scattered over the face and scalp. These blisters were then scratched and broken so that most of the involved area became covered with a wet, purulent exudate. Anorexia developed and the baby seemed sick, but the temperature was not recorded. Twenty-four hours before admission, his left eyelid became extremely swollen.

Examination on his admission to the hospital showed that most of the scalp and face was covered with thick and slightly hemorrhagic crusts, with an underlying seropurulent exudate. About the edges of these crusts, several distinctly umbilicated pustules could be seen, which appeared to be of more recent development. They were 2 to 3 mm. in diameter, on an erythematous base, and their contents were purulent. The lesions were entirely confined to the face, scalp and neck. The skin around the lesions was edematous, and the left eye was swollen shut. Lymphadenopathy was present in the left supraclavicular region. No lesions of the mucous membrane were present. The rest of the examination gave no remarkable results, except that the child was irritable but did not appear gravely ill. An irregular fever, with the temperature reaching as high as 103.2, subsided by lysis in about four days after admission.

A urinalysis gave negative results, and the blood count showed a moderate hypochromic anemia, with a white blood cell count as high as 43,000 leukocytes per cubic millimeter with 70 per cent polymorphonuclear cells. Tuberculin and Wassermann reactions of the blood were negative and a culture of the blood was noncontributory. Culture of material from the cutaneous lesions yielded a mixture of beta hemolytic streptococci and Staph. aureus. Passive transfer tests for the underlying eczema showed a positive reaction to cow's milk and to egg.

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18. Andervont, H. B., and Friedenwald, J. S.: Case of Vacciniform Blepharitis Due to an Atypical Herpes Virus, Bull. Johns Hopkins Hosp. **42**:1, 1928.

19. Service of Dr. Mitchell I. Rubin.

On treatment with 1:8,000 potassium permanganate on compresses and sulfathiazole by mouth and locally in the form of a 5 per cent ointment in an emulsion base, gradual but steady improvement occurred. Except for scarring and the underlying eczema, the skin was clear in about three weeks.

Eleven months after the acute illness, when there had been no signs of eczema for about nine months, it was considered safe to vaccinate the patient. A typical nonimmune reaction was obtained, following vaccination with vaccinia virus by means of the multiple pressure method.

## VIRUS STUDIES

*Isolation of the Virus.*—Material was secured from several pustules of the patient by means of capillary tubes and immediately rubbed over the scarified cornea of a rabbit. An ocular infection accompanied

Fig. 1.—The appearance of the patient on the day after admission (one week after onset of Kaposi's varicelliform eruption). Umbilicated pustules are still visible about the mouth near the margin of the crusted areas.

with moderate pyrexia occurred, which was characteristically like that produced by herpes simplex. The rabbit recovered and was reinoculated one month later (intraperitoneally) with known herpes simplex virus (HF strain). It survived after the reinoculation, thus establishing the fact that the rabbit was immune to herpes virus.

Attempts were made to isolate the virus by corneal inoculation with material from vesicles on the mother's face and with saliva from the father and brother. All were unsuccessful.

*Neutralization Tests.*—Venous blood was collected from the patient during the acute stage of the disease and again three weeks later. Samples of the blood were taken at the same time from the mother, father and brother, and all samples were tested on the same day.

The tests for neutralizing antibodies were made on mice according to the technic of Scott and others,[20] as follows:

From mouse brains infected with HF strain of herpes virus, a 10 per cent emulsion was made in nutrient broth; it was centrifuged, and tenfold dilutions were made with the same diluent. Each dilution was mixed with an equal amount of the undiluted serum to be tested. After incubation for one hour at room temperature and one to three hours at refrigerator temperature, the mixture was inoculated intracerebrally into each of 4 mice in 0.03 cc. amounts. The mice were observed for ten days, at which time the experiment was terminated. The neutralizing power of each serum was calculated by the 50 per cent endpoint method of Reed and Muench.[21] For purposes of standardization, a known herpes-immune rabbit serum

Fig. 2.—*A*, appearance three weeks later, showing scarring and the rough thickened skin of the underlying eczema. *B*, appearance six months later. The eczema is almost entirely cleared. Slight persistent scarring in the form of spots of depigmented atrophic skin is barely visible.

was included in each test, as was a normal rabbit serum. The serums being tested were compared with the immune rabbit serum and graded as "strong," "moderate," "weak" or absent.

*Results.*—The sample of the patient's serum taken at the onset of the illness showed "weak" neutralizing power, while the sample of

20. Scott, T. F. M.; Steigman, A. J., and Convey, J. H.: Acute Infectious Gingivostomatitis, J. A. M. A. **117**:999 (Sept. 20) 1941.

21. Reed, L. J., and Muench, H.: Simple Method of Estimating Fifty Per Cent Endpoints, Am. J. Hyg. **27**:493, 1938.

serum taken three weeks later had a "strong" neutralizing power. The tests with the serums obtained from the patient's brother and parents gave the following results: The initial neutralizing titers were "moderate" for the parents and "weak" for the brother. In contrast to results of tests with the patient's serum, there were no rises in titer when the tests were repeated.

## COMMENT

When we considered the information at hand concerning this case, we found that there were three possible etiologic agents. In view of the patient's close exposure to vaccinia virus through his brother and the character of these cutaneous lesions, vaccinia virus seemed the most likely. It is unfortunate that we were unable to carry out serologic tests to determine the presence of antibodies against vaccinia virus in the serum of our patient during the acute stage and during convalescence. However, we feel that the successful vaccination of the patient with a nonimmune "take," eleven months after his acute illness, together with evidence implicating the virus of herpes simplex, is strong evidence against vaccinia virus as the etiologic agent in our case.

It is well known that viruses, such as the swine influenza virus, act in association with bacterial organisms to produce disease. It is quite possible that in a similar manner the staphylococci and streptococci cultured from the lesions of our patients may have contributed to the clinical picture of Kaposi's varicelliform eruption.

Our virus studies, however, do give evidence that the herpes virus was present in the cutaneous lesions, and that during his illness herpes-neutralizing antibodies developed in his serum. The latter fact makes it highly probable that the herpes virus, which we isolated from the patient's skin, did in fact come from the vesicular lesions.

One practical point which can be made as a result of our studies is that infants with eczema should probably be protected from any one suffering from a herpes infection, as well as from persons who have been recently vaccinated.

## CONCLUSIONS

A case of Kaposi's varicelliform eruption with recovery is reported, the disease occurring in a 6 month old colored infant with eczema.

Our studies revealed that the herpes virus was present in the cutaneous lesions and that neutralizing antibodies were developed in the patient's serum during his illness. This suggests strongly that the herpes virus, possibly in association with the staphylococci and streptococci, was involved in an etiologic relationship in our case of Kaposi's varicelliform eruption.

ADDENDUM

Since this paper was written prior to extended foreign duty by two of us (W. A. J. and D. M. P.), further work has appeared in the literature on the same problem. Several authors [22] have described cases of Kaposi's varicelliform eruption, in which considerable evidence is presented that the etiologic agent is the virus of herpes simplex. Others,[23] especially Hershey and Smith,[23c] present cases and studies implicating the vaccinia virus. It may be true that both the herpes and the vaccinia virus are capable of producing the syndrome known as Kaposi's varicelliform eruption and that it is impossible at present to distinguish between the two on clinical grounds.

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22. Seidenberg, S.: Zur Aetiologie der Pustulosis vacciniformis acuta, Schweiz. Ztschr. f. Path. u. Bakt. **4**:398, 1941. Blattner, R: J.; Heys, F. M., and Harrison, M. L. K.: A Filterable Virus Isolated from a Case of Kaposi's Varicelliform Eruption, Science **99**:432, 1944. Barton, R. L., and Brunsting, L. A.: Kaposi's Varicelliform Eruption, Proc. Staff Meet., Mayo Clin. **18**:199, 1943; Kaposi's Varicelliform Eruption Arch. Dermat. & Syph. **50**:99 (Aug.) 1944. Wenner, H. A.: Complication of Infantile Eczema Caused by the Virus of Herpes Simplex, Am. J. Dis. Child. **67**:247 (April) 1944. Lane, C. W., and Herold, W. C.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **50**:396 (Dec.) 1944.

23. (*a*) Ronchese, F.: Dermatitis Vaccinica, Arch. Dermat. & Syph. **47**:613 (May) 1943. (*b*) Lutz, W.: Ueber Pustulosis vacciniformis sive varioliformis acuta, Dermatologica **86**:138, 1942. (*c*) Hershey, F. B., and Smith, W. E.: Generalized Vaccinia in an Eczematous Child, Am. J. Dis. Child. **69**:33 (Jan.) 1945.

# Case Reports

## PROLONGED TACHYCARDIA

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MILWAUKEE

THIS case of tachycardia in a child 6 years of age is presented because of the history of persistent tachycardia in the mother and because of the variable responses to the many therapeutic procedures used. Irritable heart and disturbance in heart action are not unusual in children, but they do not persist. Tachycardia may follow acute infections or emotional disturbances, particularly in hypersensitive children. Persistent tachycardia, such as occurred in this case, is rare. There are not many cases reported in the literature. Russell and Ellison in 1927 reported a case of prolonged tachycardia associated with congenital heart disease in an infant 15 months of age.[1] Review of the history of this case suggests a probable Stokes-Adams syndrome beginning at 4 months of age. Quinidine sulfate reduced the pulse rate from 300 per minute to 100 and kept the rate down for fourteen days, after which the child was discharged from the hospital. Two months later she was brought back to the hospital with a pulse rate of 240. She appeared to be perfectly well and was not distressed. There was no cyanosis. Quinidine sulfate reduced the pulse rate to 100 after three days. The further course of the patient is not known.

Mayer in 1933 reported a case of persistent tachycardia in a girl of 10 years.[2] The rapid pulse rate was noticed when the child was 1 year of age. At 2 years of age the pulse rate varied between 180 and 200. The electrocardiograms showed only the lack of respiratory influence and of premature contraction. The P waves in leads II and III were inverted, indicating that the impulse arose somewhere outside the sinoauricular node. There was no indication of cardiac damage or axis deviation. Various preparations of digitalis and quinidine were tried with no success.

In 1934 Field, Barker and Alexander reported a case of unusual sinus tachycardia in a man 40 years of age, which was thought at first to be paroxysmal auricular tachycardia and which led to advanced

1. Russell, H. B., and Ellison, J. B.: A Case of Prolonged Tachycardia, Associated with Congenital Heart Disease, in a Child 15 Months Old, Lancet **2**:546 (Sept. 10) 1927.

2. Mayer, W. F.: Persistent Tachycardia in Girl Aged 10, Pennsylvania M. J. **36**:527 (April) 1933.

congestive heart failure.[3] The usual methods of interrupting the attack failed, and the vagus nerves were exposed in the neck and stimulated electrically. There was no demonstrable effect on the heart. Subsequently, partial heart block with digitalis slowed the ventricles and produced improvement. Eventually the auricles slowed, the heart block disappeared and the patient recovered. The authors felt that the tachycardia was in reality an extreme sinus tachycardia due to failure of vagus inhibition.

In 1935 Leriche, Bouchut and Froment reported 1 case of a severe type of apparently primary sinus tachycardia which greatly resembles the cases of pronounced tachycardia in hyperthyroidism.[4] This type is benign in that it does not entail auricular fibrillation, hypertensive heart disease or hypertrophic cardiopathy and does not lead to heart failure, but it proves obstinate as far as treatment is concerned; sedation of the sympathetic system does not influence the syndrome, and confinement to bed is only transitorily effective, the tachycardia recurring immediately when a certain activity is resumed. The sympathetic disequilibrium can be improved permanently only by a carefully balanced progressive physical retraining, according to Gallavardin. As a rule, the condition of such patients does not change much in the course of years, and neither considerable improvement nor considerable aggravation will supervene. Although this condition is in no way threatening to life, it creates so much discomfort and incapacitation that an attempt to deal surgically with it seems justified, as medical treatment has proved unsatisfactory. As a sympathetic disturbance is to be assumed as the primary cause of the condition, it seems logical to think of intervention on the pathways through which the accelerating impulses are conveyed to the heart.

The case of Leriche and his associates concerned a man, aged 31, who had suffered an attack of rheumatic fever at the age of 20 in the course of his military service. Subsequently breathlessness persisted, and at first a diagnosis of endocarditis was made, but later the diagnosis was changed to that of persistent tachycardia with extracardial murmur. The patient was able to do his work, but he had to avoid effort which provoked dyspnea and tachycardia. Quinidine sulfate was administered but was of no avail. Because of the condition it was decided to carry out a hemithyroidectomy, which seemed indi-

3. Field, H., Jr.; Barker, P. S., and Alexander, J.: Unusual Sinus Tachycardia with Observations on Vagal Activity: Direct Electrical Stimulation of the Vagus Nerves in Man, Am. Heart J. **9**:298 (Feb.) 1934.

4. Leriche, R.; Bouchut, L., and Froment, R.: Bilateral Stellectomy for Intense and Obstinate Sinus Tachycardia: Surgical Result After 18 Months; Pathologic Observations on the Conditions of the Thyroid Gland and the Stellate Ganglia, Presse méd. **43**:1041 (June 29) 1935.

cated by the patient's aspect and by the increased basal metabolic rate. The operation was performed with the area under local anesthesia; the thyroid gland was found to be small and firm. Histologic examination of the specimen showed essentially normal thyroid tissue with some irregularities of the size of the vesicles and very slight sclerosis; signs of hyperthyroidism were absent. No improvement whatsoever followed this operation. Three weeks later an extirpation of the left stellate ganglion was carried out, but no notable improvement followed this intervention. Two months later the right stellate ganglion was extirpated. Histologic examination of the ganglions showed punctiform hemorrhages and capillary dilatation, in all likelihood due to the operative handling. Apart from these changes, however, changes of the nerve cells were also present; some of the cells presented a protoplasm which stained poorly or had irregular contours. Satellite cells were more frequent than normal at certain places. The connective tissue capsule of the ganglions showed blood vessels with decided infiltration of lymphocytes and plasmocytes in their adventitia and in the perivascular sheath, comparable to the conditions encountered in inflammatory processes. In the interior of the ganglions, vessels surrounded by a cuff of lymphocytes were also encountered, and it was in the surrounding of these vessels that the satellite cells were most numerous, so that an aspect of pseudoneuronophagy was almost created. According to the pathologist's report, slight alterations of definitely inflammatory character were demonstrable in the ganglions, although their etiologic interpretation was impossible.

After the second stellectomy the spontaneous attacks of paroxysmal tachycardia no longer occurred. When the patient was at rest the pulse rate varied between 80 and 90, and when he was standing or walking it rose to 110 to 130. Six weeks after operation, the patient felt well and the pulse rate did not exceed 100 when he was up. He was able to walk without attacks of paroxysmal tachycardia, although the pulse rate rose to 130. Two and a half months after the last operation the patient was able to walk slowly without any discomfort; he suffered from frequent vasomotor attacks of several minutes' duration, with redness of the face and pallor of the hands and feet, accompanied with malaise but without tachycardia. Six months after operation, moderate effort still provoked an acceleration of the heart rate to 140, with palpitation but without dizziness. Shortly afterward a sudden attack of tachycardia with a pulse rate of about 180 supervened and was followed by distinct vasomotor disturbances at the level of the face. For weeks then the attacks recurred but were less violent than before operation. Several months later, the attacks became more frequent; tachycardia was less predominant, however, than the sudden attacks of vasodilatation, which concerned the upper part of

the body but left the upper limbs almost completely free. These attacks suggested a cicatricial neuroma of the sympathetic nerves, and an infiltration of the region of the stellate ganglion with procaine hydrochloride was carried out; it was followed by an attack within half an hour, but afterward the patient felt relieved. Two weeks later mental disturbances in the form of polymorphous deliriant ideas supervened, and the patient had to be transferred to a neurologic department, where he quickly calmed down. The intervals between the attacks became longer, and the patient was satisfied with his condition. At rest the pulse rate varied between 70 and 85; a certain instability of the pulse rate was due to the patient's emotionalism. Slight effort caused the pulse rate to rise to 100, but the resting rate was restored within three minutes. One and a half years after the last operation the patient was in good general condition, his resting pulse rate was 80 and his basal metabolic rate was 12 per cent above the norm.

From the point of view of symptomatology, the case in question was a typical one; from the point of view of etiology, it represented the characteristics of an acquired tachycardiac neurosis, which, according to Gallavardin, is the rarest type. Before the attack of rheumatic fever the patient had not even exhibited a nervous temperament. The pathogenesis of the condition was less clear than the cause. The role of rheumatic fever in the appearance of the condition would suggest a cardiac lesion, but neither on clinical nor on roentgenologic or electrocardiographic examination could any anomaly be found. Origin of the tachycardia in the thyroid was contradicted by the absence of thyroid hypertrophy, the type of tachycardia, the paradoxic reaction to iodine treatment, which caused a considerable rise of the basal metabolic rate, a characteristic of nervous tachycardia according to Gallavardin and Tourniaire, and the observations on thyroidectomy. A disturbance at the level of the sympathetic system had therefore to be assumed as the etiologic factor of the tachycardia, and this conception is well supported by the histologic findings in the extirpated ganglions. It would probably have been preferable to extirpate the right stellate ganglion first, as it has been shown that probably the right sympathetic ganglion acts particularly on the sinus node while the left one acts chiefly on the atrioventricular node. Actually, left stellectomy was of no avail, while right stellectomy was followed by immediate improvement. Seven months after operation, however, a recurrence took place, accompanied with pronounced vasodilatation, and for seven months the patient's condition was not very satisfactory; vasomotor attacks persisted and were complicated by attacks which resembled asthma and were relieved by epinephrine. The tachycardia was much attenuated during this period, however, and at times even a bradycardia of 50 to 60 beats per minute was observed, accompanied

with a sensation of emptiness in the head. Fifteen months after operation, the condition became more favorable than ever before and the patient felt well; he presented the aspect of a nervous person who readily reacts with moderate tachycardia but whose condition was absolutely compatible with a normal life. It may be expected that the success will be a permanent one, as observation has shown that the result of operations on the sympathetic system appears late but is then progressive. The case shows that severe tachycardia neurosis with sympathetic signs and increased basal metabolic rate may occur in the absence of any macroscopic or microscopic changes of the thyroid gland and may be due to an inflammatory process in the sympathetic chain.

Morgan,[5] discussing the management of paroxysmal tachycardia in 1943, stated:

> Paroxysmal supraventricular tachycardia is a common functional heart disorder of all ages but particularly of young adults without organic heart disease. Relatively few attacks are seen by physicians, since attacks cease spontaneously or the patient has learned ways of stopping them. Of the persons seeking medical aid for this arrhythmia, a few find their attacks resist ordinary physical means and oral therapy and persist for hours and sometimes many days before they spontaneously cease. Deaths have been recorded, as have hemiplegia and gangrene, as thrombotic sequelae of the low pulse pressure and minute output during such attacks.
>
> Advice for the prevention of attacks is principally directed to extracardiac somatic factors and these vary with the individual patient. If drugs are indicated because attacks are frequent and tend to persist and annoy the patient, quinidine is best, but an occasional patient responds better to digitalis. Sedatives are helpful in the physician's program of reassurance and sometimes are all that is required when observant patients realize that a contemplated experience may precipitate an attack. . . .
>
> It is recognized that the psychic factor is a great one in these problems from several angles. It may act as a direct precipitating factor for attacks and a healthy person may develop an incapacitating neurosis because of ill founded notions of the significance and prognosis of his disorder. Reassurance, therefore, must be definite and backed by proved ability to terminate attacks as promised. The published facts are that people have been known to have attacks for over 50 years and have no influence on longevity, and if organic heart disease exists, the prognosis depends on the underlying heart disease. . . .
>
> Some form of carotid sinus reflex elicitation will stop the majority of attacks. The patient deserves to be carefully instructed in carotid sinus pressure, ocular pressure, the Mueller and Val Salva experiments and told about the benefits of postural change and vomiting. These six physical procedures in addition to some schemes which his experience may have taught him provide an armamentarium which in itself offers more than passive reassurance. Pressure on the eyeballs has to be enough to cause the patient some discomfort and the patient should look down while pressure is exerted. The Mueller and Val Salva experiments are easy for the patient to execute without notice, since in

5. Morgan, P. W.: The Management of Paroxysmal Tachycardia Including the Use of Mecholyl, Ann. Int. Med. **19**:780 (Nov.) 1943.

one the patient strains to exhale but keeps his glottis closed and in the other he strains to inhale but keeps his glottis closed. Various combinations of these procedures have caused slowing of paroxysmal fast heart rates when single procedures have failed. To induce vomiting, apomorphine [apomorphine hydrochloride] has been used and syrup of ipecac in doses of from one to four drachms [4 cc. to 16 cc.] has been a favorite of some good clinicians as a treatment of attacks.

When the physical methods have been tried or before trying them, the patient can be instructed to take his usual dose or a double dose of quinidine at two hour intervals for two or three doses or until tinnitus is noticed. In this manner patients have tolerated as much as 100 grains [6.5 Gm.] in one day. If there is any tendency for him to develop an apprehensiveness, he should be provided with an effective sedative which he can take early in the attack and allow himself to assume a semirecumbent or recumbent position unless he knows that such positions tend to bring on attacks. It has been thought that not until such procedures have been well tried and heart tones are becoming less vigorous or signs of basal râles or very annoying systemic signs have appeared, was one justified in using parenteral quinidine or mecholyl or intravenous strophanthin or digitalis. One reported attack of 10 days' standing, several years ago, was stopped with 15 cat units of digitalis intravenously when quinidine had failed. Just recently intravenous metrazol has been used with satisfactory results. . . . The drip method of intravenous quinidine administration is the safest, but it takes such a long time that one can wonder whether it was quinidine or the passage of time which stopped the tachycardia. In the choice of any heroic procedure it is comforting to know that the effects of the drug can be quickly stopped at any moment, and in that regard mecholyl has an advantage over the others.

For terminating attacks mecholyl, now council accepted for this purpose, is advised in the War Department's Technical Manual entitled "Notes on Cardiology in Aviation Medicine. . . ."

The use of the various cholines has been a development of the present age. . . . Acetyl-beta-methylcholine or mecholyl is one of the few cholines stable enough and with sufficient investigation behind it to deserve a place in our therapeutic armamentarium. When it reaches the tissues it is probably in a form which duplicates products of the body itself. Its greatest usefulness is in treating paroxysmal supraventricular tachycardia, and it has no place in treating other arrhythmias. It has been used in persons of all ages from infancy to old age. Atropine or epinephrine will abolish its effects and quinidine tends to block its action. Oral administration has been unsatsfactory either to prevent or stop attacks. Mecholyl should never be given intravenously, since the effects of hypodermically administered therapeutic doses are so rapid and dramatic that anyone who has not been appraised of them should familiarize himself well with the effects, and should not undertake to use the drug unless he very carefully follows a set procedure. However, if this is done, the physician can avail himself of an effective agent which he can control at will. . . .

Since the effect of mecholyl on the bronchial tree is to cause bronchial spasm, it has been suggested that in asthmatic subjects the drug be either not used or else even greater care than usual be employed. In hyperthyroid patients mecholyl is capable of inducing auricular fibrillation and for this reason hyperthyroidism is sometimes considered a contraindication for this therapy. . . .

The patient receiving mecholyl should be recumbent, since the erect posture at the height of the drug's action may cause fainting. A bed pan should be

ready for the same reason in case the subject should have a sudden desire to defecate during the drug's action which is a possibility though none of my patients has had more than active audible peristalsis.

It is well to explain to the patient and to any relatives who insist on being present during the treatment each of the subjective and objective manifestations of the mecholyl effect before giving the injection. In less than a minute a brilliant flush comes in a wave over the blush areas, perspiration and salivation are profuse and peristalsis becomes audible. Even if appraised before, the patient usually makes some comment concerning these things because they come so quickly. A medical colleague whose tachycardia I terminated with mecholyl without a previous sedative was so impressed that he decided to refer any resistant tachycardias for such therapy, and he volunteered the suggestion that the use of such a drug should be in the hands of someone other than a general practitioner such as himself. Having used the drug both with and without the previous administration of a sedative, I believe it is better to administer something to dim slightly the perceptive senses before using mecholyl. For this he has used a therapeutic dose of morphine sulphate. . . .

The average dose of mecholyl for adults is 20 to 50 milligrams and it is available in sealed glass ampoules of the dry drug, each containing 25 milligrams. The contents of each ampoule are easily soluble in 1 cc. or less of sterile distilled water introduced into the ampoule. So that no confusion arises one can either use differently marked syringes or place the empty mecholyl ampoule over the needle of the syringe filled from it. Atropine gr. 1/50 (0.4 mg.) in solution ready for intravenous injection is in the second syringe. The arm with easily accessible veins is selected and a blood pressure cuff is applied or good tourniquet placed loosely high on the upper arm. Mecholyl is then administered subcutaneously below or distal to the blood pressure cuff which is not inflated. At the moment the heart rhythm and rate return to normal as detected by the stethoscope over the precordium, the blood pressure cuff is inflated to prevent further absorption and to make a vein ready if desired for the administration of atropine. The return to sinus rhythm has occurred in my experience as early as 80 seconds following the mecholyl injection and has been reported in less time. If no effect on rate is noted by the time the drug is at its peak effect as manifested by flush in the blush areas, perspiration, salivation and loud peristalsis (2 to 10 minutes) Starr has suggested massage of the site of injection and also carotid sinus stimulation by one of the above physical means. This is necessary in some 20 per cent of cases. If no effect is manifest 30 minutes after the injection, another dose can be given. The drug does not lose its effectiveness by repeated use as indicated by a report of its successful use in stopping 15 of 16 attacks recurring in a child over a two year period. I have had a similar successful experience in eight attacks out of nine in a middle-aged woman over a three year period. The first time it was used on this patient it was ineffective because only 25 milligrams were given and no second dose was used and later experience demonstrated that 40 to 45 milligrams were needed. On several occasions she had 8 to 10 grains of quinidine within three hours of satisfactory mecholyl treatment, which supports the statement that mecholyl can break through the quinidine effect. The reliability and short time necessary to abolish the tachycardia which this woman has been having occasionally for 25 years have made her grateful. Most of her attacks cease spontaneously or with repeated oral doses of quinidine, but if they persist for a few hours, she now has them stopped whereas previously she has been incapacitated at least a day or two. In a middle-aged man whose attack had

resisted usual therapy for 10 hours a second dose of 60 milligrams reinforced with carotid pressure was given with success after one of 40 plus carotid sinus stimulation plus massage of the site of injection had failed.

No deaths have been reported from the use of the drug, but reports are available of great overdose (10 and more times the therapeutic dose)[6] and mistaken intravenous administration, and in each instance recovery was complete. . . .

In each attack that I have treated with mecholyl the rapid rhythm was interrupted by a brief period of asystole, then the next few beats seemed slightly slower than the normal sinus rhythm, which was quickly established. The quick transition from a heart rate of 160 to 180 to one of 70 or 80 with the brief asystole is usually noted by the patients, though the relief from the rapid rate is ample reward for the brief moment of what they have termed a "funny feeling."

Howard reported a case of paroxysmal tachycardia in an infant in the fourth day of life and reviewed the literature on this condition in the newborn.[7] His patient responded well to digitalis and was well at the end of one year.

### REPORT OF A CASE

L. A. M., a 6 year old girl, was admitted to the hospital on Feb. 9, 1944, with the complaint of rapid heart beat. The child had always been in good health until February 1943, when she had a severe infection of the upper respiratory tract, which lasted five days and which was treated with sulfonamide compounds. In September 1943 another severe infection of the upper respiratory tract developed. In November the patient became listless and "could not keep going." After this illness she suffered from a pain in the chest. The mother took the pulse rate and found it to be very rapid. On December 17 the child became ill with "the flu" complicated by otitis media. From that time on the pulse was very rapid, and the patient was kept in bed after December 17. In January 1944, three weeks prior to her entrance to the hospital, tincture of digitalis was prescribed, 5 drops four times a day, which was increased one week later to 10 drops four times a day. Four days after the increased dose was started vomiting and diarrhea developed, and the use of digitalis was discontinued.

The only significant feature in the past history is the fact that the mother, aged 36 years, has paroxysmal tachycardia. Any emotional upset may precipitate an attack, during which she becomes totally incapacitated, weak and listless and extremely agitated. Her pulse rate will then range between 160 and 200. The father is a husky, healthly athlete. The patient has a sister 6 months of age, who appears to be perfectly normal.

On examination this child was observed to be thin, hyposthenic, calm, agreeable and cooperative, with a pulse rate of 126 beats per minute. She had no complaints. The blood pressure was 115 systolic and 70 diastolic. There were no heart murmurs. There was no capillary pulse visible. The extremities were warm and had a normal color. No other abnormalities were found.

The first day after admission, February 10, the pulse rate was 140, and pressure on the eyeballs slowed this rate to 80 beats per minute. The urine showed a faint trace of albumin, acetone and acetoacetic acid and 6 white blood

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6. Peterman, M. G.: Congenital Megacolon, J. Pediat. **27**:484 (Nov.) 1945.

7. Howard, P. J.: Paroxysmal Tachycardia in an Infant the Fourth Day of Life: Recovery with Digitalis, J. Pediat. **26**:273 (March) 1945.

cells per high power field. The blood count was: hemoglobin content 13 Gm., red blood cells 5,900,000 and white blood cells 9,600, of which 29 per cent were polymorphonuclears, 1 per cent eosinophils, 2 per cent monocytes, 59 per cent small lymphocytes, 7 per cent large lymphocytes and 2 per cent plasma cells. The sedimentation rate was normal, and Wassermann and Kline blood tests gave negative results for syphilis. Reaction to a tuberculin test was negative, and to the Schick test, positive. The patient was given phenobarbital, 0.032 Gm. every six hours. An electrocardiogram showed the T waves in leads II and III merged with the P waves but probably inverted. The tracing was compatible with the clinical impression of paroxysmal tachycardia (fig. 1).

On February 11 the blood pressure was 118 systolic and 72 diastolic and the pulse rate at midnight in sleep was 80. On February 12 the pulse rate at 8 a. m. was 112; at 10 a. m. the rate was 156. The urine was normal. Mecholyl (acetylbetamethylcholine bromide), 0.005 Gm., was given subcutaneously every six hours. Syrup of ipecac was also given, 4 cc. every six

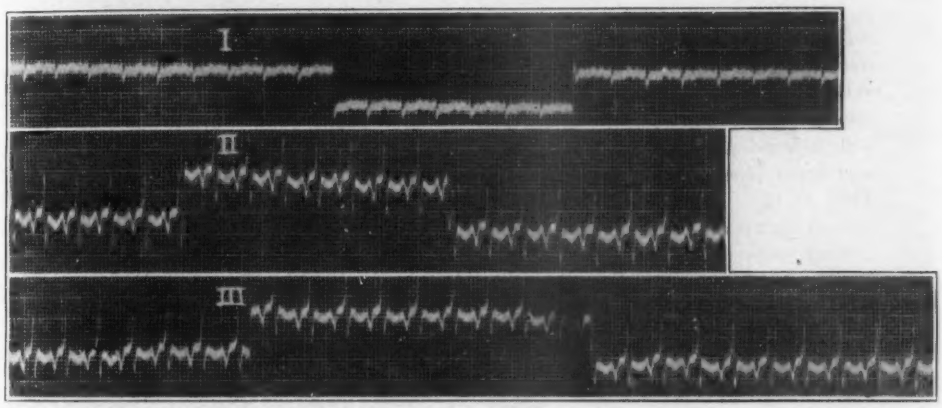


Fig. 1.—Inversion of T waves in leads II and III.

hours. On February 13 the urine showed a faint trace of albumin. Quinidine sulfate, 0.032 Gm., was given every three hours. The pulse rate seemed to slow down; however, on February 14 the pulse rate was 150. Pressure on the eyeballs stopped only a few beats. The syrup of ipecac and the mecholyl bromide were discontinued. On February 16 papaverine hydrochloride was given, 0.008 Gm. three times a day for two days, and this dose was doubled on February 18. The pulse rate continued to be rapid. On February 17 the blood pressure was 96 systolic and 74 diastolic and the pulse 150. On February 18 the urine showed a trace of albumin; the pulse rate was 160. On February 19 the pulse rate was 160, and pressure on the eyeballs produced no change. Mecholyl bromide, 0.005 Gm., was given subcutaneously at 4:15 p. m., with the following results: The pulse rate at the time of injection was 148; five minutes later, 156; ten minutes later, 164; fifteen minutes later, 160; twenty minutes later, 152; twenty-five minutes later, 105; thirty-five minutes later, 88; forty-five minutes later, 84; fifty-five minutes later, 90. On February 20 the pulse rate was 150 to 160.

On February 21 the pulse rate was 160 at 10:40 a. m., and pressure on the eyeballs reduced this rate to 100 with skip beats which persisted for twenty-five minutes. Quinidine sulfate was increased to 0.065 Gm. every three hours. On

February 22 there was no apparent effect from the quinidine sulfate; the pulse rate was 146.

On February 23 the pulse rate was 168. An electrocardiogram showed the following data: the rate regular but faster than on February 10 and an increased amplitude of T waves, which were the only changes since February 10. On February 24 the pulse rate was 168.

On February 25 a blood pressure cuff was wrapped around the patient's neck and the pressure in the cuff was raised to 140 mm. of mercury. The pulse rate gradually slowed down to 68. Five minutes later it was 80, and it remained at that rate for fourteen hours; at that time the patient was suddenly awakened for medication and the pulse rate increased to 160. Mecholyl bromide, 0.025 Gm., was given orally every six hours. On February 26 the pulse rate remained at 160. The mecholyl bromide was increased to 0.025 Gm. every four hours. On February 27 the pulse rate was 184.

On February 27 Dr. M. F. Rogers was called in consultation. He made the following interpretation of the electrocardiogram:

"An electrocardiogram taken today explains the mechanism occurring during periods of severe tachycardia. 1. At the time of pronounced tachycardia, rate 160 to 180, there is an ectopic rhythm arising outside the sinoauricular node. When the rate is in the neighborhood of 110, the rhythm arises within the sinoauricular node. 2. On stimulation of the carotid sinus through pressure with a blood pressure cuff, the ectopic rhythm is abruptly halted. An auriculoventricular block occurs, followed by slow rhythm of normal sinoauricular origin. This, in turn, is followed at times by excitation of the irritable focus outside the sinoauricular node, with two complexes indicating (*a*) aberrant bundle branch conduction or (*b*) a less likely irritable focus causing a ventricular contraction. 3. This, in turn, may be followed by a return to the type shown in 1; gradually, however, there occurs a bigeminal rhythm, consisting of two cycles starting in the sinoauricular node and competing with normal bundle branch conduction (at times there is a third), which, in turn, is followed by a stimulus arising again outside the sinoauricular node (as it did during the first rhythm), which is blocked and reveals no ventricular response—therefore the pause noted clinically" (fig. 2).

On February 27 there was no response to the increased dosage of mecholyl bromide; the amount was further increased to 0.050 Gm. every four hours. On February 28 the pulse rate continued to be rapid in spite of the mecholyl bromide, which was then discontinued. Cedilanid[8] was then administered, 0.5 mg. every twelve hours. On March 2 the hemoglobin content was 12 Gm., the red blood cell count 4,300,000 and the white blood cell count 5,800. The pulse rate was 130 and regular. Magnesium sulfate, 5 cc. of a 10 per cent sterile solution, was given intravenously with no effect.

On March 4 Dr. M. F. Rogers noted: "The heart rate is still fast, and there are no significant changes in the electrocardiogram. In the interval since Cedilanid[8] was started there has been no evidence of digitalis intoxication. I believe that the use of digitalis should be continued, the dose being increased by 1 tablet every fourth day but an electrocardiogram being secured before each increase, and the changes in the interval and the T waves being noted for digitalis effect. Should nausea, vomiting, visual disturbance, diarrhea or prostration occur, of course it should be stopped immediately."

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8. Cedilanid is a glucoside of digitalis leaves; each tablet contains 0.5 mg. of lanatosid.

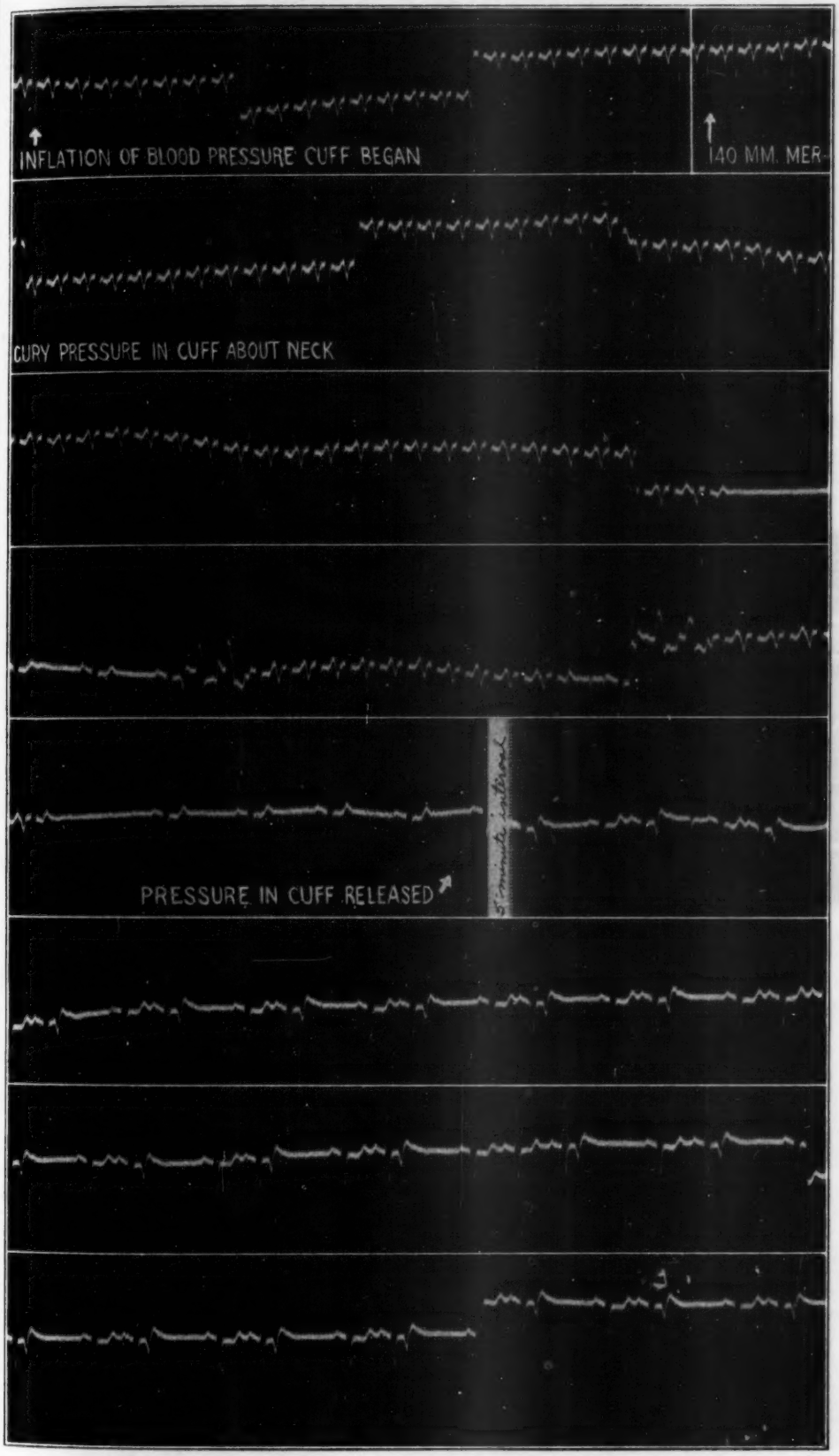


Fig. 2.—Rate 160 to 180, ectopic rhythm arising outside the sinoauricular note. When the rate is around 110, the rhythm arises within the sinoauricular node.

On March 5 there was regular arrhythmia, 4 slow beats followed by 9 to 13 fast beats. On March 8 the pulse was 84 per minute and regular. The electrocardiogram as interpreted by Dr. Rogers revealed the following data: "This shows some ectopic focus in the auricle with bundle branch block for one to two complexes, after which the ectopic auricular focus is followed by normal branch conduction and tachycardia" (fig. 3).

On March 10 the pulse rate continued at 84, and Cedilanid was given, 1 mg. per day. On March 11 the Cedilanid was increased to 2 mg. per day. On March 14 the pulse rate was 100. On March 16 the electrocardiogram showed marked improvement, with some digitalis effect still but otherwise within normal limits. On March 18 the pulse rate was 84 and irregular. On March 20 the blood count was: hemoglobin 12.5 Gm., red blood cells 4,450,000 and white blood cells 6,600. On March 23 the pulse rate was 160 and irregular. The patient was discharged from the hospital with instructions to continue the use of Cedilanid, 0.5 mg. twice a day. On April 21, 1944 the pulse rate was

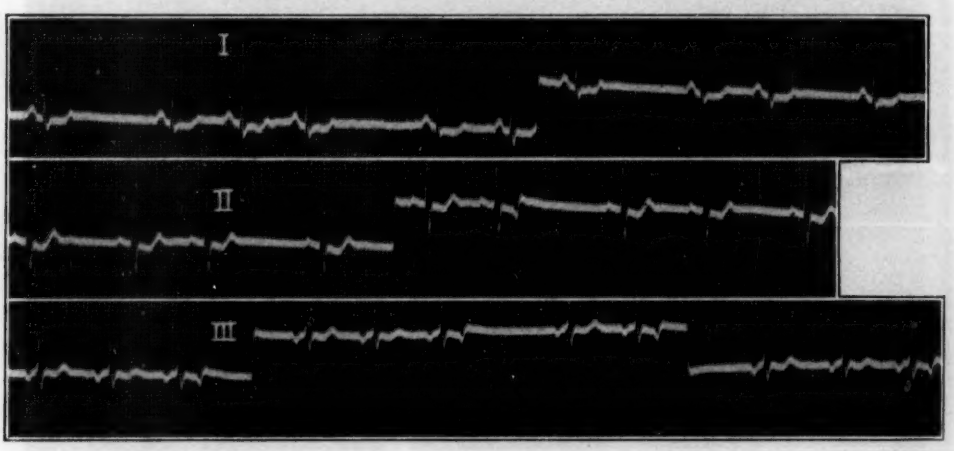


Fig. 3.—Ectopic focus in the auricle, with bundle branch block for one or two complexes.

120 and irregular; there were no complaints. Cedilanid, 0.5 mg., was given in the morning, and 0.25 mg., at night.

On May 13, 1944 the pulse rate was 140, with intervals of 80, lasting three to five minutes. The bending test (the trunk bent to a right angle for ten seconds) produced no change in the heart rate. Cedilanid was prescribed, 0.5 mg. twice a day. The patient then moved to another state.

The child was examined Feb. 6, 1945 by Dr. L. F. Hill, Des Moines, Iowa, who reported that the heart was perfectly regular. One month later an irregularity was present again. However, Dr. Hill reported that the child looked well, felt well and had a good appetite. She had been going to school regularly throughout the winter months and had missed only two days, when she had a cold. She returned to my office June 8, 1945. The parents reported that "the rate stayed down to normal as long as the child received 2 Cedilanid tablets a day. It returned promptly to the rapid rate when the dose was reduced to 1 tablet." The child seemed to be stable, well developed, well nourished and in excellent physical condition. The pulse rate was 166 but perfectly regular. Dr. M. F. Rogers also saw the patient and reported a pulse rate of 200 which

was essentially regular. The apnea test gave a negative reaction. The veins on the backs of the hands emptied at shoulder level. The electrocardiograms revealed an auricular tachycardia arising outside the sinoauricular node, interrupted at times by a noticeably slow rhythm which originated in the sinoauricular node. There was no disturbance of auriculoventricular or intraventricular conduction (fig. 4). Teleroentgenograms and fluoroscopic study and esophagrams by Dr. J. E. Habbe, revealed a vertically placed heart, which was rather broad across the base toward the left, with moderate fulness of the pulmonary artery but with no raising of the apex of the heart. The cardiac area measured 73.5 sq. cm., which was 18 per cent above the predicted normal of 62 sq. cm.

The patient was discharged with directions to continue the use of Cedilanid, 0.5 mg. twice a day. On June 23 the pulse rate was 166 and the blood pressure

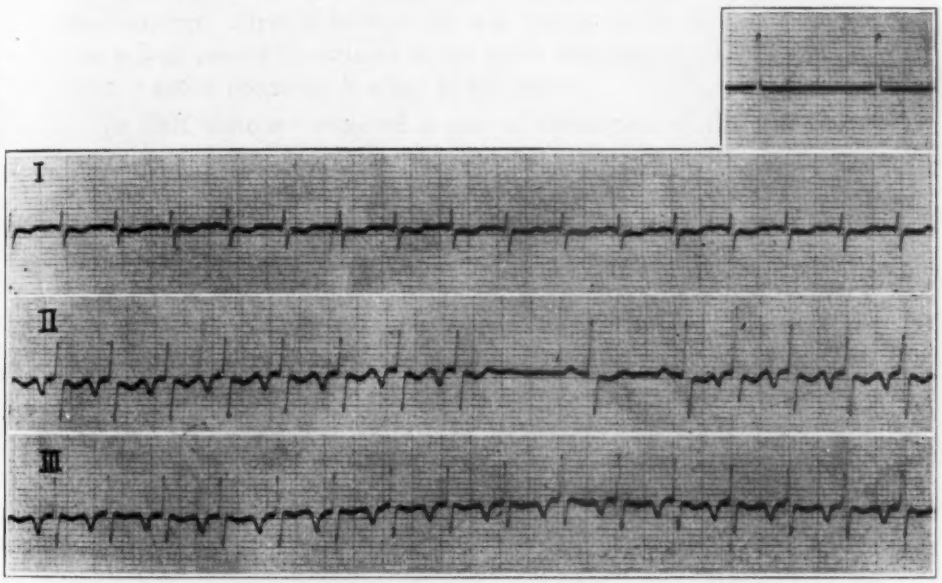


Fig. 4.—Auricular tachycardia outside the sinoauricular node. No disturbance of auriculoventricular conduction.

108 systolic, 80 diastolic. Pressure on one or both eyeballs slowed the pulse down to 70 to 80, or five or six beats, after which it immediately returned. to the former rate. The patient was given Cedilanid, 0.5 mg., three times a day.[9]

## CONCLUSIONS

This case of persistent tachycardia is reported because of the history of paroxysmal tachycardia in the mother and because the tachycardia did not develop in the patient until after several attacks of infection of the upper respiratory tract. At first the patient responded promptly

9. An electrocardiogram on Jan. 3, 1946 shows tachycardia still present, arising part of the time in the sinoauricular node and part of the time outside.

to the oculocardiac reflex and to vagus stimulation. There was no response to absolute rest in bed and sedation. There was no response to digitalis to the point of intoxication. There was also no response to large doses of mecholyl bromide. Cedilanid produced results at various times; however, there was an interference with the rapid rhythm and the development of an irregularity; namely, brief periods of asystole followed by a rhythm slower than the normal sinus rhythm.

411 East Mason Street (2).

# THROMBOSIS OF THE PULMONARY ARTERY IN CHILDREN

## Report of a Case with a Review of the Literature

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NEWPORT NEWS, VA.

THROMBOSIS of the pulmonary artery with complete occlusion is a rare condition in children. Fourteen cases have been reported in the literature. First to be reported was that of Dickinson,[1] in 1897. It was a fatal case of thrombosis of the trunk and main branch of the pulmonary artery occurring in a boy of 4½ years.

In 1901 Guinon [2] reported a case of thrombosis of the pulmonary artery in a 2 year old child who had miliary tuberculosis. Her main symptoms were extreme cyanosis and dyspnea. At autopsy, large tracheobronchial nodes were found that might have been the cause of the bilateral thrombosis.

A typical case [3] of thrombosis of the pulmonary artery that occurred in an 11½ year old girl was reported by Whipham in 1911. The presenting symptoms were dyspnea and cyanosis of seven months' duration. The murmur heard over the heart was typical of a patent ductus arteriosus, although this was not discovered at autopsy, during which a polypoid thrombus was found extending from the pulmonary artery into the right ventricle. The thrombus was formed between the valves and the pulmonary artery.

In 1923 Gehrt [4] reported from Germany 7 cases of thrombosis of the pulmonary artery discovered in 600 autopsies done on children. The youngest subject was just under 2 years of age. In 2 of the cases the disease had been diagnosed before death as "la grippe," while in 5 the condition followed measles. The conclusions were that the diagnosis is difficult and the prognosis hopeless.

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1. Dickinson, L.: Thrombosis of the Pulmonary Artery in a Case of Congenital Stenosis of the Orifice, Tr. Path. Soc., London **48**:57, 1896-1897.

2. Guinon: Thrombosis double de l'artère pulmonair, Bull. Soc. de pédiat. de Paris **3**:191, 1901.

3. Whipham, T. R.: Infective Polypoid Thrombosis, Proc. Roy. Soc. Med. (Sect. Study Dis. Child.) **4**:199, 1910-1911.

4. Gehrt: Thrombose der Arteria pulmonalis im Kindesalter, Ztschr. f. Kinderh. **36**:221, 1923.

In 1931 Gordon and Perla [5] reported the case of a child in whom the pulmonary artery was almost completely occluded by vegetative thrombi firmly attached to the wall of the vessel. This patient had a Streptococcus viridans infection with patent ductus arteriosus, congenital pulmonary stenosis and hypertrophied right ventricle.

In 1941 Gunter [6] presented the history of identical twin boys, 15 months of age, who died nine days apart. The first had vomiting, diarrhea and fever which resulted in dehydration and acidosis. Death occurred during the administration of fluids parenterally. At autopsy, the right pulmonary artery was found to be completely occluded, while numerous branches of the left were also occluded. The second twin had a mastoidectomy followed by death in five and one-half hours. Thrombosis of the right major branch of the pulmonary artery was the cause of death.

Mori Chavez, [7] in 1942, added the case of a 9 year old child with the presenting symptoms of dyspnea and fever of three months' duration. The degree of cyanosis is not mentioned. The clinical diagnosis was bronchopneumonia. Autopsy revealed a thrombus completely obliterating the trunk of the pulmonary artery before the bifurcation and continuing to the branches without interruption.

## REPORT OF CASE

*History.*—A 7 year old school boy was first seen with the chief complaints of fever, restlessness, cough and abdominal pain. The illness began eight months previously with recurrent "colds," chills, fever and poor appetite. During the course of his illness he had considerable loss of weight, complained of abdominal pain, had occasional hemoptyses and was confined to bed most of the time. The only other factor of importance in the present illness was an automobile accident which occurred approximately ten days to two weeks prior to onset of the illness. While crossing a street, he was knocked down by a car, which struck his chest rather lightly. A physician found no external evidence of injury at the time.

The past history revealed that he had been considered in good health during his life, had developed normally, had walked and talked at the usual time and had been as active as his siblings. He had had the usual childhood diseases, except scarlet fever, diphtheria, pneumonia and rheumatic fever. The family history was essentially normal. His mother and father were alive and well, as were 3 siblings. There was no history of contact with tuberculosis. The history by systems was essentially normal except for nocturia with the onset of the present illness; the urine then appeared dark, the "color of tea."

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5. Gordon, H., and Perla, D.: Subacute Bacterial Endarteritis of Pulmonary Artery Associated with Patent Ductus Arteriosus and Pulmonic Stenosis, Am. J. Dis. Child. **41**:98 (Jan.) 1931.

6. Gunter, J. V.: Thrombosis of Pulmonary Artery in Identical Twins, Arch. Path. **31**:211 (Feb.) 1941.

7. Mori Chavez, P.: Trombosis progresiva obliterante de la arteria pulmonar, Rev. peruana de pediat. **1**:98 (Dec.) 1942.

*Physical Examination.*—When the patient was first seen, eight months after the onset of his illness, physical examination showed him to be acutely ill. He was thin and pale, with prominent ribs. The temperature was 102 F. rectally; the pulse rate was 120, and respiration rate was 48 per minute. The skin was pale and dry. No rash was evident. There was moderate cyanosis of the lips, mucous membranes and nail beds. The lymphatic system was involved only to the extent of enlarged, firm anterior and posterior cervical nodes. The scleras appeared blue; the conjunctivas were pale. The nose was clear, and the pharynx was injected. The heart was enlarged to the left and decidedly enlarged to the right. A thrill was felt over the third left interspace. A loud, harsh systolic murmur was heard all over the precordium, loudest over the aortic and pulmonic areas. The lungs showed dulness over the entire right side anteriorly and posteriorly, with bronchial breathing and increased breath and voice sounds over these areas. The left lung was clear. The edge of the liver was tender and enlarged to 4 fingerbreadths below the costal margin. The spleen was palpably enlarged and tender. The extremities showed clubbing of the fingers. There was slight edema of the ankles.

*Laboratory Data.*—The hemoglobin value was 40 per cent; red blood cell count, 2,210,000, and white blood cell count, 17,250, with 86 per cent polymorphonuclear leukocytes, 11 per cent lymphocytes and 3 per cent monocytes. No malarial organisms were found on a blood smear. A serologic test for syphilis elicited a negative reaction. Results of a culture of the blood were negative. Results of agglutination tests for typhoid (O and H antigen), paratyphoid A and B, Brucella abortus and Proteus X-19 were all negative. The icterus index was 15. Gastric analysis late in the illness revealed no tuberculosis organisms. Urinalysis gave the following results: specific gravity, 1.014; reaction, acid; albumin, a trace; reaction to tests for sugar and bile, negative; white blood cells and red blood cells, a few; and casts, none. Reaction to a tuberculin test (Mantoux) was negative five days after admission.

*Roentgenographic Examination.*—A roentgenographic examination of the chest, Sept. 17, 1943 (eight months after the onset of illness), gave the following data: The diaphragm was smooth and regular, and its angles were clear. The right lung showed an extensive amount of infiltration, spotty in type, extending from the level of the first rib to the diaphragm in the inner zone of the lung. The left lung showed a mild amount of infiltration spreading from the hilus. The diagnosis was that this process appeared to be a rather extensive pneumonitis and that tuberculosis should be ruled out.

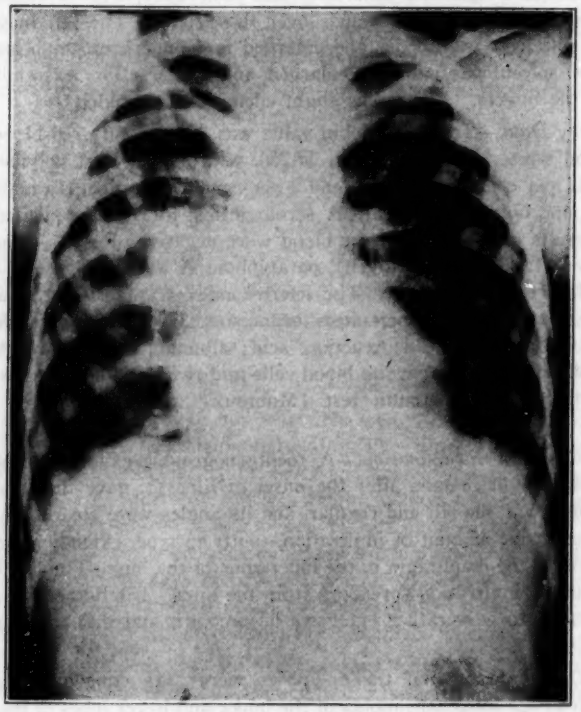
*Diagnoses.*—On admission the diagnoses were: (1) congenital heart disease, type undecided; (2) lobar pneumonia of the upper and lower lobes of the right lung; (3) chronic passive congestion of the liver and spleen, and (4) pronounced secondary anemia.

*Treatment.*—Sulfadiazine was given in adequate doses. Six transfusions of 200 to 250 cc. each of citrated whole blood were administered.

*Course in the Hospital and Subsequently.*—The temperature varied from 95 to 96 F. rectally each morning to 104 F. each afternoon. Respirations were always rapid, ranging from 24 to 50 per minute, although they were usually around 32. The pulse rate varied around 128 per minute. No improvement was actually noted at any time. The blood level of sulfadiazine reached 13.9 mg., but since no effect was evidenced, sulfadiazine therapy was stopped on the twenty-fifth hospital day. The clinical course did not change after the cessation of the sulfadiazine therapy. The right lung showed no changes, but soon the left lung showed moist rales and dulness over the hilar area posteriorly. The heart remained unchanged, while the liver

and spleen remained large and tender. Report of a roentgenographic examination of the chest October 2, was as follows: "The appearance shows very little change from that shown on the first plate, taken on September 17. Diagnosis: Because of the lack of any change in this process, tuberculosis is more probable.

The patient was discharged to his home one month after admission, unimproved. There his condition remained unchanged. A roentgenogram taken two weeks prior to death revealed the same data as previously, except that what appeared to be three areas of cavitation with questionable fluid level were apparent in the lower lobe of the right lung. Twenty-five days after discharge he had two convulsions of a generalized nature and died on the way to the hospital.



Roentgenogram of the chest.

*Gross Observation at Autopsy.*—Gross observations on the day of death are reported as follows: On inspection the body was that of a fairly well developed but emaciated white boy. Rigor mortis was present to an extreme degree. The body had been embalmed, the axillary vessels having been used. Distinct clubbing of the fingers of both hands was present. No other abnormalities were seen on the surface of the body except that the abdomen was more prominent than normally.

Section: Section was made from the suprasternal notch to the symphysis pubis.

Peritoneal Cavity: The surfaces of the peritoneal cavity were normally smooth, moist and glistening. The appendix was normal in location and appearance. Approximately 100 cc. of clear fluid was present in the dependent portions of the cavity and in the pelvis. The mesenteric lymph nodes were not enlarged.

Pericardial Cavity: A small amount of fibrinous exudate was seen in the upper portions of the cavity about the great vessels at this point. An excess of fluid (75 cc.) was present in the cavity, and this showed the presence of small bits of fibrin. The surfaces in the lower portions of the cavity were smooth.

Pleural Cavities: The left lung was free in its cavity. The right lung was adherent to the chest wall laterally, and this adherence was most apparent in the region of the lower lobe. The lung could be easily removed, however, as the exudate was fibrinopurulent in character.

Heart: The heart was increased in size rather appreciably, with the right side showing the most involvement. On section, an opening was seen in the interventricular wall. This opening was high in the cavity, so that the left ventricular opening was just below the aortic valve. The mitral, tricuspid and aortic valves were normal in appearance. The pulmonary artery was filled with a laminated thrombus, which filled the spaces back of the pulmonic valve flaps and extended slightly into the right ventricle. The thrombus was present in the right branch, so that it extended into the pulmonary tissue, practically occluding the vessels which enter the lower lobe, with extension into one branch in the lower portion of the upper lobe. The thrombus appeared to have occluded the entire lumen of the pulmonic artery, making it difficult to conceive of any blood being able to enter either lung. The left branch of the artery, however, appeared to be slightly opened. The wall of the artery just above the valves was pouched so that the outer surface of the vessel was nodular in appearance. The wall in the pouched portions was thin.

Lungs: The left lung was voluminous and contained air throughout except at two points in the lower lobe where infarcts were present. The pulmonary tissue was extremely edematous. The upper lobe of the right lung was solid, and a portion of the lower lobe was similar in consistency. On section, the plugged branches of the pulmonary artery could be seen in these portions. Softened areas, some with small cavities, were seen, from which purulent material escaped. The upper portion of the upper lobe contained air, and edema of the tissue was noted. The surface of the lung over the solid portions showed fibrinous exudate attached.

Spleen: The spleen was greatly increased in size, measuring 16 cm. from pole to pole. It was firm in consistency, and on section the splenic tissue was extremely congested.

Adrenal Glands: The adrenal glands were normal.

Kidneys: The kidneys were normal in size and shape. The capsule of each stripped readily, leaving smooth surfaces. On section the kidney tissue was congested, but it was otherwise not remarkable. The pelves and ureters were normal. The urinary bladder was normal.

Gastrointestinal Tract: The stomach and large and small intestines were normal throughout.

Liver: The liver was greatly increased in size, with the lower margin on a level with the umbilicus. It was firm in consistency. On section, the hepatic tissue was congested and resembled nutmeg. The gallbladder and bile ducts were normal.

Pancreas: The pancreas was normal.

*Pathologic Observations:*—The following pathologic conditions were noted: (1) congenital anomaly of the heart (opening in interventricular wall), (2) thrombosis of the pulmonary artery with massive pulmonary infarction, (3) abcesses of the lower lobe of the right lung, (4) extreme edema of the lungs, (5) acute fibrinous pleurisy, (6) pronounced hypertrophy and chronic passive congestion of the spleen and liver, (7) ascites and (8) emaciation.

### INCIDENCE

The incidence of thrombosis of the pulmonary artery is much greater after middle life. Moller, cited by Brenner,[8] found in 1932 unselected autopsies that the incidencce was 0.9 per cent. Billings, also cited by Brenner,[8] found an incidence of 0.7 per cent in 1,700 autopsies. Brenner [8] found, however, 28 instances in 100 unselected autopsies. A survey made by Rosenthal [9] fits in most interestingly with the instances mentioned. He found that there was a decided increase in the incidence of thrombosis and pulmonary embolism in central Europe in general, as well as in surgical clinics. He felt that the accentuation was most prominent during the period of inflation, 1919 to 1924, when there was an increase in the cardiac and vascular diseases due to hunger, nervous irritability and lack of vitamins. There was no rise in the incidence of thrombosis or embolism in the United States or Canada during that period. The largest series [4] of cases reported among children, in an article dated 1923, came from Germany.

### PATHOGENESIS

The pathogenesis of the diseases may be twofold, as described by Balboni [10]: (1) primary in the vessels, as in syphilis or following influenza, rheumatic fever, allergies, schistosomiasis of the pulmonary arteries, Str. viridans infection [11] and sclerosis of the pulmonary artery, and (2) secondary. This is the commoner cause. Examples are atherosclerosis of the larger arteries resulting from conditions producing an elevated pulmonary arterial pressure, such as chronic asthma, tuberculosis,[12] pulmonary fibrosis,[13] carcinoma of the lung,[14] pleural adhesions, mitral heart disease, patent ductus arteriosus, polycythemia vera.[14a]

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8. Brenner, O.: Pathology of Vessels of Pulmonary Circulation, Arch. Int. Med. **56**:211 (Aug.); 457 (Sept.); 724 (Oct.); 976 (Nov.); 1189 (Dec.) 1935.

9. Rosenthal, S. R.: Thrombosis and Fatal Pulmonary Embolism: Comparison of Their Frequency in Clinics of Central Europe and North America with Special Reference to Increase, Arch. Path. **14**:215 (Aug.) 1932.

10. Balboni, V. G.: Multiple Pulmonary Thrombi Associated with Cyanosis and Right-Sided Cardiac Hypertrophy, New England J. Med. **223**:896 (Nov. 28) 1940.

11. Fowler, W. M.: Obliterating Thrombosis of the Pulmonary Arteries, Ann. Int. Med. **7**:1101 (March) 1934.

12. Savocool, J. W., and Charr, R.: Thrombosis of Pulmonary Artery, Am. Rev. Tuberc. **42**:57 (July) 1941. Pou, J. F., and Charr, R.: Thrombosis of Pulmonary Artery, Am. Rev. Tuberc. **37**:394 (April) 1938.

13. Wade, J. L.: Advanced Pneumoconiosis with Pulmonary Artery Thrombosis, West Virginia M. J. **36**:69 (Feb.) 1940.

14. Behrents, E. G.: Obturator Thrombosis of Right Pulmonary Artery and Necrosis of Entire Lung with Hilar Bronchogenic Carcinoma, Arch. Path. **33**:259 (Feb.) 1942.

14a. Poll, D.: Thombosis of Pulmonary Vessels in Polycythaemia Vera, J. Mt. Sinai Hosp. **1**:254 (March-April) 1935.

Arterial occlusion following contusion is uncommon, but it has occurred,[15] owing to blunt injury, without fracture or deep laceration. Wounds to arteries may be of three types[16]: (1) contusion, (2) severance of the adventitia and media with the intima bulging and (3) complete division of all coats of the vessel. An injury to the shoulder in a 36 year old[15] patient produced an incomplete bilateral thrombosis of the pulmonary artery which was compatible with life for three years.

The role played by the injury in our patient is an uncertain but probable one. The patency in the interventricular septum caused no cyanosis, since the flow of blood was from the left to the right ventricle. With the formation of the thrombus and increased pressure in the pulmonary system, a reversal of flow from the right to the left would intensify the cyanosis already being caused by the decrease in aeration of the blood in the lungs. The abscesses visualized on roentgenographic examination in the lower lobe of the right lung and discovered at autopsy were evidently the cause of the septic nature of the temperature. The terminal convulsions were due to the anoxemia caused by obliteration of the remaining channel of the pulmonary artery.

Brenner,[8] in his article, cited Hart's suggestion that when the stem of the pulmonary artery is gradually plugged by a slowly forming thrombus the circulation through the lungs may be maintained by the widening of the collateral anastomotic channels between the pulmonary artery and the bronchial vessels. Once, however, complete blockage of the pulmonary artery has occurred, the collateral channels cannot maintain sufficient circulation, since the blood entering the right side of the heart will be unable to leave it. When, as in our case, a patent interventricular septum is present, the blood which enters the right side of the heart may pass through to the left side and be carried through the dilated bronchial arteries to the pulmonary capillaries. The patient then is able to live but is profoundly cyanosed. In experiments on dogs[9] it has been noted that the systemic blood pressure is not reduced until the cross sectional area of the stem of the pulmonary artery has been reduced from 61 per cent to 86 per cent and death does not occur until the area has been reduced to 96 per cent.

## SYMPTOMS AND SIGNS

The duration of symptoms of thrombosis of the pulmonary artery may be from several minutes to one or more years. The onset may be acute, with vomiting, perspiration, cyanosis, weakness and frequently

15. Perry, T. T.: Acute Arterial Thrombosis Following Contusion, Proc. Staff Meet., Mayo Clin. **18**:19 (Jan. 27) 1943.

16. Fletcher, E. T. D., and Raven, R. W.: War Wounds and Injuries, Baltimore, Williams & Wilkins Company, 1940, p. 262.

collapse. Precordial pain is usually a presenting symptom, but the pain may be anywhere in the chest. The commoner onset,[17] and that found in our case, was with dyspnea (found in 90 per cent of the cases),[18] cough, hemoptysis and increasing cyanosis. There may or may not be previous organic heart disease.

The heart usually shows a rapid regular rate with an accentuated pulmonic second sound. There may be a to and fro murmur over the pulmonic area. The heart may be enlarged even though no independent heart disease exists. Signs and symptoms of right-sided heart failure develop during the course of the disease. Unilateral pleural friction rub may be present. Death is usually due to progressive failure of the heart, although it can be sudden if a thrombus rapidly closes a patent foramen ovale. In the reported cases of adult patients death is frequently due to some other disease. Leukocytosis is commonly present, but there is usually no absolute change in the differential count. A roentgenogram may show a particularly dense shadow over the thrombosed pulmonary artery.[8]

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis for children is more difficult than for adults. It includes: 1. Heart failure with chronic passive congestion.[18a] Here there are a moderately enlarged, smooth, tender liver, a relatively normal blood picture, dependent edema and other signs and symptoms of heart failure. The steadily increasing cyanosis found in thrombosis of the pulmonary artery is not found in heart failure. 2. Congenital heart disease. In this condition there are cyanosis, clubbing of the terminal phalanges of the fingers and toes, chronic cough and easily induced dyspnea. Polycythemia is common in cases of extreme cyanosis. Retarded physical growth and development are also found. The history is a great aid in diagnosis; however, a sudden increase in all the symptoms, particularly the cyanosis and dyspnea, should lead one to suspect thrombosis of the pulmonary artery. 3. Pneumonia. This disease is usually characterized by sudden onset, high temperature, expiratory grunt and cough. The respiratory movements are increased. Examination of the heart gives normal results. Roentgenographic and physical observations usually determine the diagnosis. The condition is an acute one, which rapidly goes on to improvement or death. 4. Tuberculosis. The pneumonic type of tuberculosis may be confused with thrombosis

17. Kampmeier, R. H.: Thrombosis of the Main Branches of the Pulmonary Artery, J. Thoracic Surg. **3**:513 (June) 1934.

18. Middleton, W. S.: Abdominal Pain in Pulmonary Thrombosis, Ann. Int. Med. **18**:345 (March) 1943.

18a. Kugelmass, I. N.: Clinical Pediatrics, New York, Oxford University Press. 1943, p. 135.

of the pulmonary artery. It is characterized by irregular fever, sweating, pallor, asthenia, enlarged spleen, lymphadenitis and positive reaction to a tuberculin test or the presence of tuberculous organisms in the gastric content.

### TREATMENT

In prolonged cases, treatment should be directed toward the relief of symptoms, especially dyspnea and cyanosis, by means of complete rest in bed and administration of oxygen as needed. There are no contraindications to small transfusions in cases of severe secondary anemia. Diet should be consistent with the age of the patient and the factor of rest in bed. Additional vitamins should be supplied as needed. Operative therapy is not feasible at the present time.

### PROGNOSIS

For adults it is difficult to give a prognosis. Death may occur within fifteen minutes, or spontaneous recovery [19] may result. Experimentally, the prognosis may be predicted by readings of arterial and venous blood pressure; a rising arterial pressure is favorable, while an increase in venous pressure is unfavorable.

In the reported cases in children, the mortality has been 100 per cent.

### SUMMARY

Fourteen cases of thrombosis of the pulmonary artery have been reported in the literature, and a fifteenth case is reported in this paper. The patient was a 7 year old boy whose symptoms, of seven months' duration, followed an automobile accident causing contusion of the right chest. The presenting symptoms and signs were cyanosis, dyspnea, fever, cough, hemoptysis and abdominal pain. This picture simulated a pneumonic process of the right lung, with right-sided heart failure. Severe secondary anemia persisted despite therapy. Tuberculosis was ruled out. The condition showed no improvement at any time. Death occurred after two convulsions, probably of anoxemic origin.

The origin of thrombosis of the pulmonary artery is twofold: (1) primary in the vessels or, more commonly, (2) secondary to a disease process outside the pulmonary vessels. Our case falls into the second category.

The incidence is higher after middle age. A high rise in the incidence of thrombosis of the pulmonary artery was noted during the years of inflation and economic distress following World War I in Central Europe. The largest number of reported cases appeared in

19. Crawford, B. L., and Mohler, H. K.: Clinical and Pathological Study of Acute Pulmonary Embolism and Thrombosis, Pennsylvania M. J. **40**:1020 (Sept.) 1937.

1923 from Germany. It will be interesting to note the incidence of the condition in war-torn areas during and following World War II. Treatment is symptomatic.

## CONCLUSIONS

1. Thrombosis of the pulmonary artery of medical origin in children is rare.

2. The diagnosis is difficult.

3. The mortality rate is 100 per cent.

Thirty-first and West Avenues.

# Obituaries

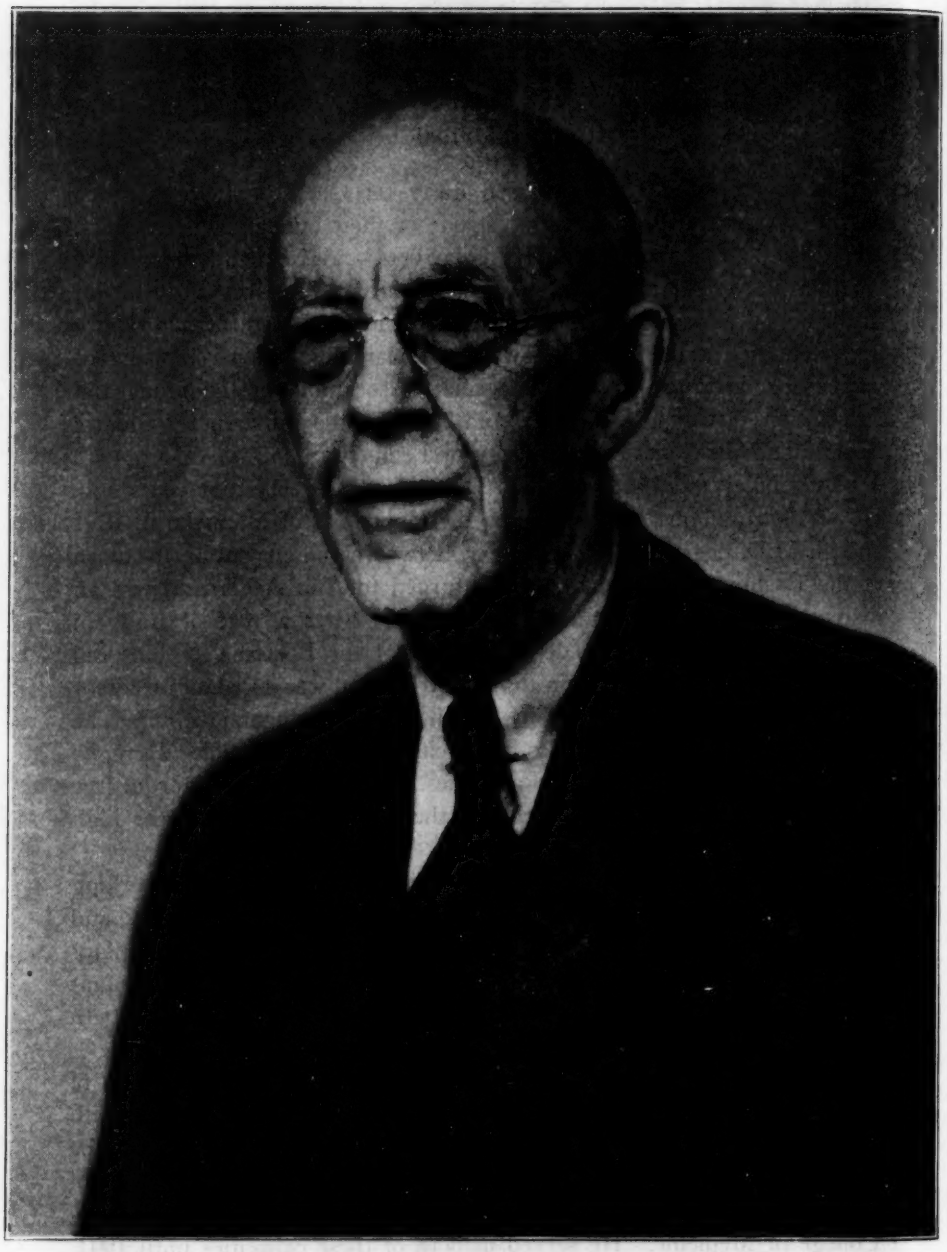
## THOMAS BENTON COOLEY, M.D.
## 1871-1945

Thomas Benton Cooley passed away on Oct. 13, 1945. In his passing, American pediatricians lost one of their outstanding members. Dr. Cooley came from a family of lawyers and frequently wondered whether he would not have made a better lawyer than a doctor of medicine. It was this legal streak that made his judgment and advice important in the deliberation toward the planning and development of various pediatric projects in the former Association for the Study and Prevention of Infant Mortality and later in the American Pediatric Society and the American Academy of Pediatrics.

Dr. Cooley was born in Ann Arbor, Mich., seventy-four years ago. He was granted an A. B. degree by the University of Michigan in 1891 and an M.D. degree in 1895. The next two years he spent as an intern at the Boston City Hospital. He returned to Ann Arbor and was an instructor in medicine from 1898 to 1900. After a year of study in Germany, he served as resident physician at the Boston City Hospital for a year. He returned again to Ann Arbor and was assistant professor of hygiene from 1903 to 1905. With this fundamental training, he started the practice of pediatrics in the city of Detroit in 1905. Here, he left his imprint by his many activities. As medical director of the Babies' Milk Fund, he was active in the campaign to reduce the high infant mortality in Detroit.

He was one of a group of young pediatricians that started working together with health officers, public health nurses, social workers and laymen in the Association for the Study and Prevention of Infant Mortality. This work played a great role in the reduction of infant deaths from the diarrheal diseases in the early decades of the twentieth century.

In World War I, he was assistant chief of the Children's Bureau of the American Red Cross. He served in France and was presented with the Cross of the Legion of Honor by that country in 1924. In 1921, he became chief of the medical services of the Children's Hospital of Michigan and, in 1936, professor of pediatrics at Wayne University College of Medicine. He served in both of these capacities until 1941, when he was made emeritus chief and emeritus professor. In 1940, the University of Michigan conferred on him the honorary degree of



THOMAS BENTON COOLEY, M.D.
1871-1945

Doctor of Science. He was one of the charter members of the Central States Pediatric Society and of the American Academy of Pediatrics; he was a member of the American Pediatric Society, and he served both of the national societies as president, acting with rare good judgment on many committees of these organizations.

Dr. Cooley made many excellent contributions to pediatric literature. The most outstanding of these were on the hematology of childhood. The contribution for which he will best be remembered is his report on a series of cases of splenomegaly, with anemia and peculiar bone changes now known as Cooley's anemia, which was presented in its original form before the American Pediatric Society in 1925. This he later called "erythroblastic anemia." This represents one of the outstanding contributions to hematology by an American. His contribution on anemia in Brenneman's "Practice of Pediatrics" shows him at his best in this special field. More recently, he had been working on a more extensive monograph on the hematology of childhood. It is to be hoped that the almost finished work can be completed by one of his associates.

He is survived by a daughter, Emily H. Cooley, and a son, Thomas M. Cooley, who, true to the family tradition, is a lawyer.

Dr. Cooley was a rare character; his high ideals, his modesty and his willingness to see the best in the motives of the other man made him generally beloved. He was not, however, easy to know, and he was most appreciated by his lifelong friends. The pediatricians who worked intimately with Dr. Cooley during the past forty years will miss him most.

# Abstracts from Current Literature

## Hygiene; Growth and Nutrition; Public Health

ACTIVITIES OF THE DIVISION OF MATERNAL AND CHILD HYGIENE. HUGO V. HULLERMAN, Illinois M. J. **88**:39 (July) 1945.

The author gives a general review of the method used by the Division of Maternal and Child Hygiene of the Illinois Department of Public Health. Its present activities are discussed, and its fields of future emphasis are indicated.

BARBOUR, Peoria, Ill.

## Prematurity and Congenital Deformities

SALMONELLA TYPHIMURIUM INFECTION IN PREMATURE INFANTS. JAMES WATT and ELIZABETH CARLTON JR., Pub. Health Rep. **60**:734 (June 29) 1945.

A small outbreak of Salmonella typhimurium infection in a nursery for premature infants is described. The infection was introduced by a child, presumably infected at birth, and was then spread to 4 children in adjacent bassinets and to 1 in a nearby bassinet. Cases were identified by use of rectal swabs plating directly to S. S. agar and to tetrathionate enrichment broth. Clinical manifestations varied from a rapidly fatal illness to mild, almost asymptomatic, infections. Control measures consisted of repeated cultural surveys of the whole ward, isolation of all infants found to harbor salmonellas and such general measures as effective washing of the hands after handling any child.

LESLIE, EVANSTON, ILL.

CEPHALOTHORACOPAGUS MONOSIMETRIC MONSTERS. EDESIO PAES BARRETO, Rev. de ginec. y d. obst. **1**:95 (Sept.) 1942.

The author reports on a cephalothoracopagus monosymmetric monster born at Pedro II Hospital.

LOZOYA, México, D. F., Mexico.

## Newborn

AETIOLOGY OF HAEMOLYTIC DISEASES OF THE NEW-BORN. R. J. WALSH, M. J. Australia **2**:33 (July 14) 1945.

Walsh studied the relationship of blood group factors, especially the Rh factor, to the causation of hemolytic disease of the newborn in 107 instances of the disease. The mother had Rh-negative blood and the infant Rh-positive blood in 92 per cent of the families investigated. An Rh agglutinin was found in the serum of 48 per cent of the mothers examined. The severity of the disease in the infant was not related to the presence of Rh agglutinin in the mother. The frequency of occurrence and the severity of the disease generally increased with an increasing number of pregnancies, although some exceptions were noted. From the evidence so far available, there is no necessity to postulate a placental abnormality or damage as being responsible for the immunization of the mother. The presence of the agglutinin in the colostrum was demonstrated in 3 of 4 cases studied. It seems possible that the presence of the Rh agglutinin in the colostrum and milk may account for the late onset of the disease in some cases. The lack of correlation between the titer of the Rh agglutinin in the mother and the severity of the disease in the child, particularly when the mother has a high titer of the agglutinin and the anemia of the infant is of mild degree or even absent, may be due to the presence of an extracorpuscular Rh substance in the fetus which absorbs some Rh agglutinin before it reaches the Rh-positive erythrocytes.

In this series there were 9 cases of hemolytic anemia in which the mother's blood was Rh positive. In 5 of these out of seven families investigated, there was an ABO group incompatibility, but in 2 the mother and infant belonged to the same ABO grouping. In the latter 2 cases the father had Rh-negative blood—unfortunately, the presence in the father's cells of an Hr or other agglutinogen could not be determined, owing to the lack of suitable testing serum. In the majority of cases studied, the Rh factor was not the etiologic agent responsible for repeated miscarriages, multiple stillbirths and physiologic jaundice.

Concerning the frequency of hemolytic disease in the newborn, it can be shown that in 12.7 per cent of all marriages the mother has Rh-negative blood and the father Rh-positive blood, and 90 per cent of all cases of hemolytic diseases occur in such families. If it is estimated that 1 case of hemolytic disease occurs in every 300 births, it can be calculated that of 43 infants born of a mother with Rh-negative blood and a father with Rh-positive blood only 1 infant will be affected.

GONCE, Madison, Wis.

## Acute Contagious Diseases

MENINGOCOCCIC MENINGITIS IN SANTIAGO, CHILE, 1941 TO 1943: AN EPIDEMIC OF 4,464 CASES. ABRAHAM HORWITZ and JOSE PERRONI, Arch. Int. Med. **74**:365 (Nov.) 1944.

Horwitz and Perroni report that an epidemic of meningococcic meningitis started in the port of Valparaiso in June 1941 and extended from there until it reached Santiago, a distance of about 80 miles (128 kilometers), three months later. The total number of cases recorded in Santiago from September 1941 to July 3, 1943 was 4,464. The incidence was approximately 1 case per 300 inhabitants, and the largest number of cases occurred in 1942. The disease was slightly more common in males than in females and was more fatal in infancy and old age than in the other periods of life. The fatality rate for all patients was 16.5 per cent; for infants under 4 years it was 28 per cent.

In a series of 450 unselected patients treated with sulfonamide compounds, the mortality was 9.3 per cent with sulfadiazine therapy, 10.7 per cent with sulfathiazole therapy and 13.3 per cent with sulfanilamide therapy. Toxic reactions occurred in 33 per cent of patients who received sulfanilamide and in 4.4 per cent of the patients who were given sulfadiazine.

GUTTMAN, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

DEATH CAUSED BY VACCINIA IN AN ECZEMATOID INFANT. CARL L. PETERSILGE and JOHN A. TOOMEY, Arch. Pediat. **61**:455 (Sept.) 1944.

The case of an 8 month old white boy with eczema, who was accidentally and indirectly vaccinated with smallpox from contact with the pustule of an older sister, is reported. The sister had been previously vaccinated against smallpox. The infant had always been well except for an uncomplicated eczema present since birth. Nine days after the exposure to the pustule, umbilicated vesiculopustular lesions, varying from 5 to 10 mm. in diameter, developed on the face and head. There were lesions on the face, head and eyelids and in the nares. Within forty-eight hours an eruption appeared on the extremities. The child became progressively more toxic and died on the eleventh day.

The report includes the hospital course, postmortem observations and microscopic description of the lesions.

GELBER, Los Angeles. [ARCH. DERMAT. & SYPH.]

EARLY IMMUNIZATION AGAINST PERTUSSIS WITH ALUM PRECIPITATED VACCINE. WILLIAM SAKO, W. L. TREUTING, DAVID WITT and SAMUEL NICHAMIN, J. A. M. A. **127**:379 (Feb. 17) 1945.

At monthly intervals, a series of three deep subcutaneous inoculations of alum-precipitated pertussis vaccine containing 40,000,000,000 bacilli per cubic centimeter

was administered to 3,793 infants, all of whom were under 3 months of age at time of the initial dose and the majority of whom were under 2 months. Doses used were 0.2, 0.3 and 0.5 cc. In a series of six thousand six hundred inoculations, there were 7.1 per cent systemic reactions, 8.6 per cent local reactions and 0.6 per cent abscess formation. In a series of seven hundred and three injections, these percentages were 15.2, 5.5 and 3.3. More reactions occurred after the second and third injections than after the first.

Rapid slide agglutinations done one to four months after the inoculations were completed were positive for 78.2 per cent of 1,834 infants and 81.2 per cent of 138 infants in two series. Macroscopic agglutination tests (quantitative) done in 300 cases confirmed these results. A follow-up of 500 children revealed that the greatest number (75 per cent) had positive agglutination reactions three to four months after the inoculations and that 63 per cent maintained them for at least two years. The incidence and the severity of pertussis in 1,834 immunized children were decidedly less than in 1,965 nonimmunized children.

The direction of the needle did not influence abscess formation. Deep subcutaneous injection gave a lower incidence of abscess. Use of a dry needle to prevent intracutaneous injection of material was the most important factor in preventing abscesses.

BAIRD, Wauwatosa, Wis.

ALLERGIC BRAIN CHANGES IN POST-SCARLATINAL ENCEPHALITIS. A. FERRARO, J. Neuropath. & Exper. Neurol. **3**:239 (July) 1944.

Ferraro reports the case of an 11 year old white boy in whom seizures developed two weeks after an attack of scarlet fever. The seizure was followed by temper tantrums, and within a few months the patient became "dull, stupid, unable to think coherently and awkward with his hands." Six months after the illness with scarlet fever the lad was institutionalized. He was distractable and showed impairment of attention and comprehension, and tests of his intellectual ability indicated deterioration. Speech was slurred; the deep reflexes were overactive, and there was a coarse tremor of the outstretched hands. He became dull, retarded and unclean in his habits. Typhoid vaccine was administered on two occasions. Later in the course of the illness he had a febrile illness for eight days, with fever, incontinence, stupor and frequent nasal hemorrhages. Involvement of the central nervous system was indicated by nystagmus, bilateral internal strabismus, overactive deep reflexes, ankle clonus and intermittent twitchings of the right arm and leg. Later the arms became flexed at the elbows, and both feet exhibited a strong plantar flexion. There was increased tone of the muscles of the jaw, so that the mouth could not be opened. Repeated lumbar punctures revealed an elevated spinal fluid pressure and a colloidal gold curve of 5555220000.

During the last months of his illness tube feedings were necessary. The limbs became spastic, and there were constant nystagmoid movements of the eyes. A Babinski sign was present bilaterally. Pneumonia developed, and death occurred about fourteen months after the onset of the acute exanthematous illness.

Ferraro also mentions the clinical history of a case previously reported by Winkelman. Anatomic study of tissue in both cases revealed the presence of a perivascular reaction, which was both lymphocytic and histiocytic. Lymphocytes prevailed in the less involved areas, whereas in the more severely damaged regions lymphocytes were surrounded with collars of compound granular corpuscles. Mixed with the lymphocytes here and there, especially in the areas of most intensive reaction, were elements presumably of mixed hematogenous and histiocytic origin, having a tendency to fuse together.

One interesting feature of the exudate was the extension of the microglial reaction, which could be traced from the blood vessels within the surrounding nerve parenchyma. The reaction of the microglia passed through all stages of transition to that of the compound granular corpuscle. A stage worthy of mention in this transformation was the loss of reticular appearance while the protoplasm was still compact, although the cell assumed a polygonal outline. Also, the vascular

and perivascular reactions were unusually intense, and both hematogenous and fixed elements seemed to participate. At times edema and hemorrhage were observed. Thrombi, softening and necrosis were also present on occasion.

Ferraro mentions three possible explanations of the pathologic process: a true inflammation, a degenerative disease process or an allergic reaction (hyperergic inflammation). He is inclined to view the process as an allergic reaction.

GUTTMAN, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY. III. MENINGOCOCCAL INFECTIONS. A. EXPERIENCES AT THE ST. LOUIS CHILDREN'S HOSPITAL. DAVID GOLDRING and ALEXIS F. HARTMANN, J. Pediat. **26**:1 (Jan.) 1945.

An analysis was made of 77 patients with meningococcic infections seen at the St. Louis Children's Hospital between the years 1937 and 1944. The years 1937 to 1942 represent nonepidemic, and 1943 to 1944 epidemic, years.

Certain fundamental conclusions have been drawn as more and more experience has been gained with the use of sulfonamide drugs in meningitis.

It is believed that intensive parenteral chemotherapy by the subcutaneous route is the treatment of choice for purulent meningitis during the first twenty-four to forty-eight hours or until the etiologic organism is proved to be a meningococcus and that blood levels for the first few days of treatment should range between 20 and 40 mg. per hundred cubic centimeters. This blood level of the drug, it is felt, is adequate to cope even with the most serious types of meningitis—that is, pneumococcic and influenzal. Although such intensive chemotherapy probably enhances somewhat the possibility of renal complications, when such precautions as adequate hydration, alkalization of the urine, careful records of daily intake and output and daily urine examinations are taken serious difficulties are rare. As soon as the etiologic organism is definitely established as the meningococcus and the clinical course has exhibited a favorable trend, then the patient may be safely maintained on 0.3 Gm. of a sulfonamide compound per kilogram of body weight.

It is believed that serum therapy does not sufficiently enhance the effectiveness of sulfonamide therapy to justify its use routinely.

Adequate hydration is of utmost importance, and a minimum intake of 10 per cent of the body weight in fluids per day should be maintained.

Alkalization of the urine is important, and it is believed that the easiest and most effective means is by the administration of sodium lactate either parenterally or enterally.

Accurate daily records of the patient's intake and output are important, as well as daily examinations of the urine and regular white blood cell counts, especially during the second week of chemotherapy.

There were comparatively few complications. The one most frequently encountered was a generalized arthritis which cleared spontaneously. The most serious complication which remained as a permanent residual was bilateral nerve deafness. Two cases of postinfectious encephalitis were encountered.

The uncorrected mortality rate was 14.2 per cent. If the 1 patient who died of another disease and the 7 patients who died after being in the hospital less than twenty-four hours are excluded (3 receiving no treatment), the mortality rate for the seven year period is 3.8 per cent.

AUTHORS' ABSTRACT.

INDICATIONS FOR AND LIMITATIONS OF TREATMENT OF POLIOMYELITIS. J. ALBERT KEY, J. Pediat. **26**:265 (March) 1945.

Infantile paralysis is an acute infectious disease the important feature of which is that it may damage or kill a variable number of the motor cells in the spinal cord and medulla and cause flaccid paralysis of the muscles supplied by these cells. The paralysis due to the death of nerve cells is permanent. In addition to the

permanent paralysis there is a variable amount of temporary paralysis which is due to temporary loss of function of nerve cells, and there is also a pseudoparalysis due to reflex inhibition caused by pain. The temporary and pseudoparalysis disappear spontaneously when the nerve cells recover.

There is no specific treatment for the disease, which is self limited. In a variable percentage of patients—at times over 50 per cent—there is no permanent paralysis. These patients need no treatment after the acute febrile stage of the disease has subsided. During this stage the treatment is a general medical problem and pain, if present, should be controlled by mild sedatives and the patient left alone. In the subacute stage, which begins when the fever subsides and lasts for from four to twelve weeks, there is a variable amount of stiffness or contracture of the muscles of the back and extremities and these muscles may be tender on pressure and painful when stretched. As a rule, pain and tenderness are not a prominent feature. As a result of the pain and tenderness, certain muscles may contract or shorten, and deformities may develop very early in the partially paralyzed extremities.

During this stage the most important part of the treatment is rest and prevention of contractures which stretch the paralyzed muscles. This can be accomplished with splints or plaster casts, which are applied only to the extremities which are painful or exhibit a tendency toward the development of deformities. There should be no attempt to restore power to the paralyzed muscles until the pain and tenderness have subsided, as such a procedure prolongs these symptoms. The pain and tenderness and tendency to contract may be relieved by heat, either dry or as moist packs, and the constant maintenance of the patient in a physiologic position, but this requires constant care and attention. During the subacute stage all paralyzed patients should be maintained in the physiologic position on a hard bed with small pads under the knees and a support to prevent equinus deformity of the feet. Joints may be moved daily within the limits of toleration during this stage, but this is not necessary, as permanent stiffness of joints will not develop within a few weeks. As soon as the pain and tenderness subside, the splints should be removed and the patient permitted to exercise the extremities.

During the convalescent stage, which begins when the pain and tenderness subside, a variable amount of spontaneous recovery occurs, but an effort should be made to restore power in the paralyzed muscles. This is done by muscular training and exercise. In training of the muscles, the patient is taught to use the weakened muscles and extremities as effectively as possible, and care is taken to avoid overuse of weakened muscles, which may result in further loss of power. The partially paralyzed patients are restored to their normal activities as quickly as possible, and braces and other supports are used when indicated to enable the weakened extremities to function, to prevent stretching of the weakened muscles and to prevent deformities due to muscular imbalance. The stiffness of the back and the limitation of straight leg raising usually have disappeared by the end of the stage of tenderness and contracture. If not, these conditions will disappear spontaneously and need no special treatment.

The convalescent stage may last for two years or longer and ends when further improvement in the power of the muscles ceases. This can be determined by examinations of the muscles, results of which should be recorded and which are made at intervals after the end of the acute febrile stage. During the convalescent stage, braces may be used and surgical procedures may be indicated to improve the function of the paralyzed extremities. AUTHOR'S ABSTRACT.

SERUM IN THE PROPHYLAXIS OF CONTACTS AND THE TREATMENT OF WHOOPING COUGH. JOSEPH H. LAPIN, J. Pediat. **26**:555 (June) 1945.

A wide choice of specific serum therapy is now available for the prophylaxis of contacts and for the treatment of patients with active whooping cough. The results with antitoxin, antibacterial pertussis rabbit serum, antitoxic and anti-

bacterial pertussis rabbit serum and hyperimmune antibacterial pertussis human serum have been reviewed. The results in prophylaxis and treatment of a new globulin fraction of hyperimmune antibacterial pertussis human serum are recorded. In the prophylaxis of contacts, 70 per cent of 10 intimate, familial, susceptible siblings were protected and 30 per cent had mild whooping cough. In the treatment of active whooping cough, in 44 per cent of 25 cases there was decided success, in 28 per cent moderate improvement and in 28 per cent no improvement. The use of larger doses of the serum together with sulfadiazine should result in striking success in the prophylaxis of contacts and the treatment of persons with active whooping cough.

AUTHOR'S ABSTRACT.

POLIOMYELITIS ON THE ISTHMUS OF PANAMA. CARL E. TAYLOR, New England J. Med. **230**:790 (June 29) 1944.

Seventy-two cases of endemic poliomyelitis on the Isthmus of Panama have been reviewed. The crest of the seasonal curve occurs during November, December and January—the end of the rainy season.

Poliomyelitis was two and three-fourths times as common among white persons as among Negroes. Fifty-two per cent of the white patients were 5 years of age or under, as contrasted with 85 per cent of the West Indian Negroes and 83 per cent of the Panamanians. There were twice as many males as females among the white and the Panamanian patients, but the incidence in the two sexes was equal in the West Indian Negroes.

There were five deaths, a mortality of 6.9 per cent. Most of the cases occurred in the large population centers.

AUTHOR'S SUMMARY.

MENINGOCOCCAL ENDOCARDITIS: A REVIEW. W. R. LOGAN, Edinburgh M. J. **52**:49 (Feb.) 1945.

The author mentions the fact that Warfield and Walker in 1903 reported the first case of recognized meningococcic endocarditis.

Since then 31 cases have been analyzed, and 25 other cases of meningococcus infection accompanied with heart murmurs with various stages of evidence of endocarditis have also been analyzed. The 31 cases just mentioned were proved on postmorten examination.

Logan states that such an endocarditis in fatal cases of primary meningitis is a very early endocardial change, possibly as early as three days from the onset of the illness. Other cases have been analyzed in which meningococcic endocarditis occurred without a primary meningitis. It is probable that there is a progressive increase in the colonies of bacteria as shown in the cultures of blood, which would allow one to draw the conclusion that there is endocardial infection, but Logan says that colony counts will be found higher in endocarditis than when the disease is purely an infection of the blood stream (meningococcemia).

NEFF, Kansas City, Mo.

CLINICAL EVALUATION OF DIPHTHERIA PROPHYLAXIS. JAMES GRANT, Lancet **1**:46 (Jan. 13) 1945.

Since the autumn of 1936 in Gateshead, England, there has been a high incidence of unusually virulent diphtheria following on a period of low prevalence. From 1936 to 1943, there were 2,278 clinical cases and 123 deaths (a case mortality rate of 5.4 per cent).

Systematic prophylaxis began in Gateshead in 1941 and was concentrated at first on all children under 12 years, the usual procedure being the injection of 0.1 cc. of diphtheria toxoid, alum precipitated, followed by a dose of 0.5 cc. for children under 9 years. Later the initial dose was changed to 0.2 cc. Children over 9 years were given three injections of 1 cc. each of toxoid-antitoxin floccules.

Comparison of the incidence of diphtheria in fully inoculated children with that in other children not so treated was disappointing. Full prophylaxis, according

to this study, appears to reduce the ill effects of invasion by diphtheria bacilli; however, if the prevalent strain of diphtheria organisms in a community is aggressive and virulent, as in Gateshead, there will be an appreciable proportion of clinical cases in inoculated persons, but these will be modified.

LANGMANN, New York.

A CASE OF MENINGOCOCCUS MENINGITIS IN A TEN MONTH OLD INFANT CURED BY SULFONAMIDE COMPOUNDS AND SERUM. L. VELASCO BLANCO, P. DERRIBERE and J. C. CHIENSA, Arch. am. de med. **20**:50 (Dec.) 1944.

The authors report the case of the third patient with meningococcic meningitis treated in their hospital service since 1941. All (including a 4 month old infant) have recovered without sequelae.

ABALLI, Habana, Cuba.

## Acute Infectious Diseases

ABDOMINAL MANIFESTATIONS OF RHEUMATIC FEVER: DESCRIPTION OF A RIGHT RECTUS SYNDROME. NORMAN BEITMAN, Ann. Int. Med. **22**:671 (May) 1945.

Sudden onset of sharp pain in the right lower abdominal quadrant, unassociated with nausea or vomiting but accompanied with tenderness and muscle spasm over McBurney's point, is described by the author in a report of 4 cases of rheumatic fever. The origin of the symptoms is believed to be a myositis of the rectus abdominis muscle.

READING, Galveston, Texas.

TOXOPLASMOSIS: REPORT OF OCULAR FINDINGS IN INFANT TWINS. PARKER HEATH and WOLFGANG W. ZUELZER, Arch. Ophth. **33**:184 (March) 1945.

Toxoplasmosis is a recently recognized infectious disease in human beings. Four principal types have been reported: (1) a granulomatous encephalitis, usually of congenital origin and occurring in fetal or early infantile life; (2) an acquired acute encephalitis, occurring in children; (3) an acquired acute disease resembling Rocky Mountain spotted fever, occurring in adults, and (4) a latent subclinical form, occurring in adults.

Heath and Zuelzer report the ocular changes associated with the disease in premature identical Negro twins. The symptoms appeared on the third day after birth. One of the babies died at the age of 1 month. The histopathologic observations on this twin are presented in detail. The second infant lived and was followed through the seventh month after birth. These 2 cases, in which the ocular lesions were so characteristic of toxoplasmosis, gave opportunity for study of the changes seen with the ophthalmoscope in identical twins.

SPAETH, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

STUDIES IN RHEUMATIC FEVER: THE PHYSIOLOGIC EFFECT OF SODIUM SALICYLATE ON THE HUMAN BEING, WITH PARTICULAR REFERENCE TO THE PROTHROMBIN LEVEL OF THE BLOOD AND THE EFFECT ON HEPATIC PARENCHYMA. HUGH R. BUTT, WILLIAM H. LEAKE, ROBERT F. SOLLEY, GEORGE C. GRIFFITH, ROBERT W. HUNTINGTON and HUGH MONTGOMERY, J. A. M. A. **128**:1195 (Aug. 25) 1945.

Studies were carried out on 113 subjects, 22 with active and the remainder with inactive rheumatic fever, divided into a test group and controls. Administration of sodium salicylate, in doses up to 180 grains (11.6 Gm.) daily, with sodium bicarbonate was followed by an increase in prothrombin time. In no case were hemorrhagic manifestation or a deleterious effect on the liver parenchyma noted. Blood levels of 30 to 50 mg. per hundred cubic centimeters were obtained with doses of sodium salicylate of 150 grains (9.7 Gm.) daily. The sedimentation rate was little affected by the administration of salicylates in polycyclic rheumatic fever.

Long-continued administration was followed by a slight reduction in hemoglobin level and red blood cell count. The white cell count and the urine were not affected.

BAIRD, Wauwatosa, Wis.

THE INFECTION OF TICKS (DERMACENTOR VARIABILIS) WITH PASTEURELLA TULARENSIS. J. FREDERICK BALL, J. Infect. Dis. **76**:83 (March-April) 1945.

Infected ticks feeding on immune or normal hosts lose their infection. Before losing their infection as a result of feeding, the infected ticks may inoculate the normal host, whereupon the host, if it is not immune, will acquire septicemia and infect all ticks feeding on it. Infected ticks feeding on immune hosts permanently lose their infections, and the bacteria are not transmitted to normal ticks feeding concurrently.

The blood meal causes clearing of the infection already present in ticks. Organisms acquired by feeding on the blood of animals with septicemia are not destroyed. Therefore, there must be a factor in normal blood which is complementary and necessary for the action of the bactericidal element resident in the tick. It is further supposed that septicemia removes this hypothetic factor from the blood, thus permitting invasion of the ticks by the organisms. The importance of immune animals in limiting the spread of tularemia is indicated by these experiments.

TOOMEY, Cleveland.

OXYURIASIS. M. C. PETERSON and J. FAHEY, J. Lab. & Clin. Med. **30**:259 (March) 1945.

A simplified method of diagnosing pinworm infection by use of a glass slide applied directly to the anus is described. Of 1,871 persons examined in a Minnesota state hospital, 1,100 (59 per cent) were found by use of this method to be infected with pinworm. One course of treatment with gentian violet medicinal was effective in 91 per cent of cases.

WILKINSON, Galveston, Texas.

THE TREATMENT OF RHEUMATIC FEVER WITH PENICILLIN. LOWELL A. RANTZ, WESLEY W. SPINK, HOWARD COGGESHALL and PAUL BOISVERT, J. Pediat. **26**:576 (June) 1945.

This investigation was conducted during a field study by the Commission on Hemolytic Streptococcus Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Division, Office of the Surgeon General, United States Army. Six young men suffering from typical rheumatic fever were treated with penicillin. Group A (Lancefield) hemolytic streptococci were isolated from the nasopharynx of each of the patients prior to his receiving penicillin. Salicylates were withheld from the patients during the period of penicillin therapy. Penicillin was administered intramuscularly in divided doses. The total dose given over a period of five to nine days varied between 700,000 and 1,000,000 units. Coincident with penicillin therapy, 1 patient with a mild form of the disease improved decidedly. A second patient improved, but he still had evidence of considerable activity. In the other 4 patients, there was a progressive increase in the severity of their diseases. Coincident with penicillin therapy, hemolytic streptococci disappeared from the pharynxes of all the patients. The disease was rapidly controlled by the administration of salicylates. It is concluded that penicillin will not favorably affect the course of rheumatic fever.

AUTHORS' ABSTRACT.

MENINGOCOCCAL MENINGITIS AND MENINGOCOCCEMIA IN CHILDHOOD. J. OSBORNE, WILLIAM H. ARNONE and GEORGE I. LYTHCOTT, New England J. Med. **231**:868 (Dec. 28) 1944.

A series of 72 cases of meningococcic infection in children is presented. In most cases there was a history of acute onset, ushered in by nausea and vomiting, head-

ache, stiff neck and a cutaneous rash. This rash was a valuable aid in the diagnosis of meningococcemia. Neurologic symptoms were present in all cases in which there was meningeal involvement. Whereas children under 3 years often had convulsions, older children rarely did.

The predominant type of organism was a type I meningococcus, occurring in 76 per cent of the cases in which cultures were positive. All patients were treated with sulfadiazine. The most frequent complication was arthritis, occurring in 12 per cent of the cases. Complete recovery from the arthritis resulted in all cases.

A mortality of 8 per cent occurred, all but 1 of the 6 fatal cases being of the Waterhouse-Friderichsen type. Four children with this syndrome survived.

AUTHORS' SUMMARY.

ELIMINATION OF CROSS-INFECTION. H. P. PICKERILL and CECILY PICKERILL, Brit. M. J. **1**:159 (Feb. 3) 1945.

The authors state that in the past they hesitated to admit small children to open hospital wards because of the danger of cross infection. However, there were some conditions which required hospitalization for a considerable period for corrective surgical treatment, such as cleft palate, harelip and hypospadias. They therefore acquired a large house with accommodations for 12 mothers and babies, each mother and baby being in an entirely separate room. Each room was well ventilated and was exposed to sunshine. The child was nursed entirely by his mother. No mother or baby was permitted to come into the pavilion if either had a cold, and visitors were not encouraged. Careful supervision of feeding was enforced. The mothers were encouraged to take their babies out of doors in the sunshine between operations. It was emphasized that the mothers must be happy, and if they did get upset and in an ugly frame of mind they were sent home. However, the authors' experiences were that the mothers were glad to get away from the responsibilities of household cares and cooperated splendidly in this endeavor.

In the comment it is stated that children do much better if they are in an environment to which they are accustomed and receive individual attention from persons with whom they are thoroughly familiar. The rationale of the whole scheme is based on the fact that a baby is born with a certain degree of passive immunity to its mother's organisms and that it acquires further immunity in the next few months. The purpose of this home was to prevent exposure of the patients to any organisms except the ones they had been accustomed to all of their lives. The authors state that they have had no evidence of cross infection since this scheme has been used.

BIRDSONG, University, Va.

THE PROPHYLACTIC USE OF SULPHANILAMIDE IN RHEUMATIC FEVER: PRELIMINARY REPORT. S. G. ANDERSON, M. J. Australia **1**:635 (June 23) 1945.

During the summer of 1944-1945, prophylactic therapy with sulfanilamide was commenced among 160 children convalescent from rheumatic fever. Children weighing under 42 pounds (19.1 Kg.) were given 0.5 Gm. of the drug once a day; children weighing over 42 pounds were given 0.5 Gm. twice a day. A few of the older and heavier children were given 0.5 Gm. three times a day. A blood level of 1.3 to 3.2 mg. per hundred cubic centimeters was considered satisfactory. The group of children was estimated to be equivalent to 104 patients each observed for six months. Of these, 1 child suffered from a doubtful recurrence of the disease. Of 470 control patients, 30 definitely suffered from recurrent rheumatic fever and 3 possibly from the same disease. The toxic effects of the drug were minimal: macular cutaneous rashes occurred in 13 children necessitating discontinuation of the drug in 3; nausea and vomiting prevented 3 children from continuing the treatment; persistent cyanosis in 2 patients and leukopenia below 5,000 cells per cubic millimeter in 2 more were reasons for stopping therapy.

GONCE, Madison, Wis.

BRUCELLOSIS DUE TO A SUBSPECIES OF BRUCELLA SUIS. R. VALLEDOR and A. HERNÁNDEZ, Arch. de med. inf. **13**:226 (July-Sept.) 1944.

The authors present observations on a case of brucellosis due to a subspecies of Brucella suis in a girl 7 years old.

The treatment by sulfanilamide was followed by relapses that diminished with the application of acriflavine intravenously in progressive doses.

The prevailing clinical signs and symptoms were: a very large spleen, intense anemia and feverish exacerbations, with profuse perspiration.

Recently prepared liver broth medium with a $p_H$ of 6.8 is advisable for culture.

The determination of the germ belonging to a subspecies of the species suis was corroborated by Professor Curbelo, of Habana, and Dr. E. Seligman, of the Salmonella Center in New York.

BRIBIESCA, Mexico.

MYASTHENIC SYNDROME OCCURRING WITH MALARIA. MARIO MENDEZ and MANUEL CHAVEZ, Rev. de neuro-psiquiat. **7**:335 (Sept.) 1944.

Mendez and Chavez stated that they know of no reported case in which a myasthenic syndrome occurred during malaria. They report the case of a boy of 7½ years who sustained a mild head injury toward the end of December 1943. The next day fever developed. He had a few febrile elevations of temperature on alternate days, which subsided spontaneously without specific treatment. After the last day of fever, ptosis of the left eyelid appeared and was followed a day later by diplopia. Soon afterward, ptosis appeared on the right side, associated with difficulty in mastication. One week after appearance of the ptosis, the patient had marked dysarthria for twenty-four hours. All the complaints were intensified by fatigue and were more severe toward evening. Later, bilateral ptosis developed, as well as paralysis of the right external rectus muscle, associated with febrile elevations of temperature on alternate days. The patient was admitted to the hospital and soon afterward had two febrile episodes, on succeeding days. Malarial organisms were found in the blood. The fever disappeared on treatment with synthetic medicaments. The bilateral ptosis and paralysis of the right external rectus muscle cleared up temporarily, after a diagnostic injection of neostigmine methylsulfate. During the next few days the myasthenic syndrone cleared up. The Kahn reactions of the blood of the patient and of the parents were negative. The fundi were normal, and the reaction to the Mantoux test was negative.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

## Diseases of Blood, Heart and Blood Vessels and Spleen

CONGENITAL HEART DISEASE: TRICUSPID ATRESIA AND MITRAL ATRESIA ASSOCIATED WITH TRANSPOSITION OF GREAT VESSELS: REPORT OF TWO CASES. L. J. MANHOFF JR. and J. S. HOWE, Am. Heart J. **29**:90 (Jan.) 1945.

Thirty-three cases of atresia of the tricuspid valves and 28 cases of atresia of the mitral valves have previously been reported.

The authors report 1 additional case of tricuspid atresia, associated with transposition of the aorta and atresia of the pulmonary artery, and 1 additional case of mitral atresia, associated with complete transposition of the great vessels. Other anomalies were present in each of these cases. No cases were found in the literature in which there were the same combinations of defects.

The clinical and embryologic aspects of each of these lesions are discussed.

GIBSON, Chicago.

THE REPORT OF A CASE OF IDIOPATHIC CONGENITAL (AND PROBABLY FAMILIAL) METHEMOGLOBINEMIA. ASHTON GRAYBIEL, J. L. LILIENTHAL JR. and RICHARD L. RILEY, Bull. Johns Hopkins Hosp. **76**:155 (April) 1945.

The patient was examined at the age of 19. He was blue at birth and remained so. Although he was never seriously ill, he was always in poor health. A cousin of the patient was blue at birth and remained so until his death, at 14.

The patient revealed intense cyanosis, and the retinal arteries and veins appeared almost black. His nutritional state was poor.

A sample of arterial blood was chocolate colored, and by spectroscopic examination and other methods was found to contain 18 Gm. of hemoglobin per 100 cubic centimeters, of which 46 per cent (8.5 Gm.) was methemoglobin. He was given 300 mg. of ascorbic acid daily for nineteen days. The concentration of methemoglobin fell to 1.7 Gm.; the cyanosis practically disappeared, and the capacity for work improved.

LYTTLE, Los Angeles.

CONGENITAL PATENT DUCTUS ARTERIOSUS: A THERAPEUTICALLY REVERSIBLE TYPE OF HEART DISEASE. TRAVIS WINSOR and GEORGE E. BURCH, South. M. J. **38**:132 (Feb.) 1945.

Congenital patent ductus arteriosus is a type of heart disease which may be classified as curable. The diagnostic features are outlined. Patent ductus arteriosus comprises 14 per cent of all congenital cardiac lesions. Over 288 instances of operative treatment have been reported in the literature. The operative mortality at best is 8.5 per cent. The author's indications for operation are the presence of physical and mental retardation, increasing cardiac failure and bacterial endarteritis within the ductus.

LOGAN, Rochester, Minn.

REFRACTORY ANAEMIA (FANCONI TYPE). J. V. DACIE and A. GILPIN, Arch. Dis. Childhood **19**:155 (Dec.) 1944.

The cases of two brothers with hyperchromic anemia which was resistant to all forms of treatment are described in detail. One boy died at the age of 14 years after four and one-half years of treatment. His anemia was profound during this time, with low platelet count, low leukocyte count and color index of 1.49.

Postmortem sections of bone marrow showed many fat cells with scattered hemopoietic cells lying between. The cells identified included late primary erythroblasts and normoblasts, lymphocytes and plasma cells; smaller numbers of myelocytes and eosinophils were present, but hemocytoblasts and adult polymorphonuclear leukocytes appeared to be absent. Much iron-containing pigment could be seen within phagocytic cells.

The other brother exhibited hyperchromic anemia, leukopenia, thrombopenia and autohemolyses in vitro similar in type to that found in patients with the clinical picture of nocturnal hemoglobinuria.

The author reviews the literature and describes the few case reports of familial refractory anemia.

KELLY, Milwaukee.

ERYTHROBLASTIC ANEMIA WITH BONE CHANGES IN EGYPTIAN CHILDREN. M. DIWANI, Arch. Dis. Childhood **19**:163 (Dec.) 1944.

Three cases of Cooley's syndrome are described. Two of the patients were genuine Egyptian children, and the third was a Greek child. Biopsy of sternal marrow, done in 2 of the cases, revealed a pronounced erythroblastic hyperplasia. Definite enlargement of the heart was noticed in 2 of the cases.

Roentgenologic examination showed evident generalized osteoporosis and in the skull thickening of the diploe and thinning of the inner and outer tables. In 1 case the typical "hair on end" appeared in the roentgenogram of the skull.

KELLY, Milwaukee.

BONE MARROW TRANSFUSION IN CHILDREN. LUIS S. PARADA, Pediat. Américas **2**:249 (April) 1944.

The author describes the generally accepted principles, technic and equipment of bone marrow transfusions. The author also mentions that bone marrow transfusions were done on 24 patients whose ages ranged from 3 days to 3 years.

Failures occurred in cases of badly deformed or ossified femurs and tibias. In cases of medullar condensation, transfusion was not possible.

DE LA TORRE, Rochester, Minn.

## Diseases of Nose, Throat and Ear

PAPILLOMATOSIS OF THE LARYNX IN CHILDHOOD. C. F. FERGUSON and H. W. SCOTT, New England J. Med. **230**:477 (April 20) 1944.

Fifteen patients with laryngeal papillomatosis were treated at the Children's Hospital in Boston during the ten year period 1933 through 1942. Papillomas are the commonest tumors of the larynx in childhood and are benign, self-limited growths that tend to recur but also to disappear at puberty. According to Crowe and Breitstein, the mortality from laryngeal papilloma in children under 5 years equals and possibly exceeds that of carcinoma of the larynx in adults. The incidence of laryngeal papilloma as estimated from the literature is approximately 1 case per thousand clinic patients. In this series it has an incidence of approximately 1 : 6,000. According to Gerhardt, in about one fifth of all cases the condition is congenital.

The symptoms produced by papillomas are hoarseness, aphonia, stridulous breathing, dyspnea and, later, the resultant signs of increasing laryngeal obstruction. At the Children's Hospital, the method of choice in the treatment of laryngeal papillomas is that of repeated endolaryngeal excision. In 8 of the 15 reported cases, there were excellent clinical cures, each patient having a normal voice and a normal larynx. Three patients are still under treatment, and only 1, who was discharged as normal five years ago and is now 17 years of age, has had a recurrence. Three patients died, 2 as a result of asphyxia at home and 1 of laryngeal diphtheria. Only 1 of these deaths was directly attributable to the papilloma.

GENGENBACH, Denver, Colo.

THE SPEECH HANDICAPPED. WENDELL JOHNSON, Rev. Educ. Research **14**:241 (June) 1944.

The author finds that the estimates of the number of students with defects of speech in the public schools of the United States vary according to the definitions and survey methods used and that there are more boys than girls with defective speech. He finds that there are persons with defective speech at all levels of intelligence but that they are commoner at the subnormal level. According to the studies made before 1941, pupils with speech defects were more retarded scholastically than their intelligence levels warranted, but since 1941 investigators have found there is no such retardation. Although speech correction in the United States has been developed through the public schools, only a small percentage of the needy subjects are given treatment. The author states that many textbooks and articles on speech correction have been published recently. There has been increased research in the field of speech disorders, especially in speech and language development, interrelation of speech and hearing and language behavior. The field of speech pathology has been extended in the past few years by research, and a number of authors and investigators are mentioned. The article is well documented and annotated.

FERGEN, Baton Rouge, La.

DO YOU KNOW SOMEONE WHO STUTTERS? JAMES F. BENDER, Scient. Monthly **49**:221, 1944.

The author gives a general review of the history, incidence and relationships of sex, intelligence and handedness to stuttering. Three case histories of stutterers are given as illustrations of three different corrective technics used to meet the special problems in each case. One method, concerned with stuttering due to an environmental difficulty, was informal and indirect. The other two were direct, with relearning taking place by voluntary stuttering in 1 case and by phonetic analysis by the patient in the other.

POLLACK, Evanston, Ill.

## Diseases of Lungs, Pleura and Mediastinum

THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES: I. GENERAL CLINICAL CONSIDERATIONS. MORRIS SIEGEL and L. A. JULIANELLE, Ann. Int. Med. **22**:1 (Jan.) 1945.

Sulfadiazine was given to 30 children for a period of fifteen weeks (December 1942 through March 1943); a group of 30 children served as controls.

There were no significant differences in the frequency and the severity of infections of the respiratory tract observed in treated and in control groups.

READING, Galveston, Texas.

THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES: II. GROSS ALTERATIONS IN THE NASOPHARYNGEAL FLORA ASSOCIATED WITH TREATMENT. L. A. JULIANELLE and MORRIS SIEGEL, Ann. Int. Med. **22**:10 (Jan.) 1945.

Prolonged treatment of physically normal children with sulfadiazine resulted in a rapid but temporary disappearance of the gram-negative cocci. After the reappearance of the cocci an exalted tolerance for the drug on the part of the bacteria was demonstrated. Other organisms were not noticeably affected, although a partial inhibitory action on hemolytic streptococci was noted. Pneumococci were not altered in their numerical incidence, but evidence of changes in immunologic types was noted.

READING, Galveston, Texas.

THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES: IV. TRENDS IN PNEUMOCOCCAL TYPES INITIATED BY DRUG TREATMENT. L. A. JULIANELLE and MORRIS SIEGEL, Ann. Int. Med. **22**:29 (Jan.) 1945.

During prolonged administration of sulfadiazine, types of pneumococci may acquire a high degree of resistance to the drug. Those strains which remain fast to the drug retain their virulence and specificity.

With a discontinuance of the drug, the incidence of types resumes a more normal distribution. Precipitating, agglutinating and protective antibodies were not found in either treated or untreated children.

READING, Galveston, Texas.

INHALATION OF PENICILLIN AEROSOL IN PATIENTS WITH BRONCHIAL ASTHMA, CHRONIC BRONCHITIS, BRONCHIECTASIS AND LUNG ABSCESS: PRELIMINARY REPORT. ALVAN L. BARACH, FREDERICH H. SILBERSTEIN, ENID TRIBE OPPENHEIMER, THOMAS HUNTER and MAX SOROKA, Ann. Int. Med. **22**:475 (April) 1945.

The inhalation of penicillin aerosol is discussed in detail by the authors. Its possible irritant effects on the lungs were determined. Inhalations of from 20,000 to 100,000 units per cubic centimeter did not produce harmful results. In human subjects the penicillin solution was aerolized by the passage of 5 to 8 liters of oxygen per minute through a nebulizer containing 1 cc. of penicillin in concentrations between 20,000 and 100,000 units per cubic centimeter.

Of 20 patients treated, 5 showed decided improvement and 10 others moderate improvement. Of the 15 patients who improved, 7 suffered a recurrence of symptoms in two months or less.

READING, Galveston, Texas.

DEPLETION IN ASTHMA. FRANCIS M. RACKEMANN, J. Allergy **16**:136 (May) 1945.

This is a short but excellent article, such as can be expected from Francis Rackemann. It stresses the importance of paying attention to the general condition of the patient and of seeing that he gets good food, rest and fresh air in

addition to good nursing. There are times when this attention is more important than treatment of the allergy, and often the asthma is relieved without treatment.

HOYER, Cincinnati.

VOMITING OF AN OPEN SAFETY PIN. EDWARD B. BENEDICT, New England J. Med. **230**:484 (April 20) 1944.

The successful vomiting of an open safety pin is such a rare occurrence that the reporting of a case seems justifiable. Only 3 similar cases have been found in the literature. The whole episode concerning this 3 year old girl took place within a five hour period. The fact that the point was bent toward the keeper must have facilitated the swallowing and subsequent vomiting.

GENGENBACH, Denver.

ETIOLOGIC FACTORS IN BRONCHOPNEUMONIA AMONGST INFANTS IN LONDON. G. PAYLING WRIGHT and HELEN PAYLING WRIGHT, J. Hyg. **44**:15 (Jan.) 1945.

Bronchitis and pneumonia account annually with few exceptions for the deaths of one fifth of all London infants dying under 2 years of age. Bronchopneumonia secondary to measles, epidemics of measles, pertussis or influenza accounts for about 10 to 15 per cent of this mortality. During epidemics of measles the peak of the mortality from measles was two to seventeen weeks after, and never before, that of the mortality from bronchopneumonia.

The winter rise in mortality was not associated with any comparable increase in the pneumococci or hemolytic streptococci carrier rates.

There was a strong correlation of mortality rate with substandard housing, social index and percentage below the poverty line.

Low external temperature appears to be the most important predisposing cause of fatal bronchopneumonia in infants, their weekly death rate from this disease being about seven times greater in midwinter than in late summer.

JANNER, Wauwatosa, Wis.

## Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THERAPEUTIC EFFECTIVENESS OF PENICILLIN IN TREATMENT OF VINCENT'S STOMATITIS AND ITS FAILURE TO INFLUENCE FAVORABLY CERTAIN OTHER MEDICAL CONDITIONS. J. S. SWEENEY; W. J. MORGINSON; R. W. ROBINSON and E. KILPATRICK, J. Lab. & Clin. Med. **30**:132 (Feb.) 1945.

Forty-three patients with Vincent's stomatitis were treated with from 600,000 to 1,000,000 units of penicillin given in doses of 25,000 units intramuscularly every three hours. In all cases prompt recovery resulted. A number of other medical conditions for which penicillin was less effective or entirely ineffective are mentioned. The list of these diseases includes furunculosis, acne vulgaris, asthma, malaria, rheumatic fever, subacute bacterial endocarditis and others.

WILKINSON, Galveston, Texas.

CONGENITAL ALKALOSIS WITH DIARRHEA. JAMES L. GAMBLE; KATHLEEN R. FAHEY; JANET APPLETON and ELSIE MACLACHLAN, J. Pediat. **26**:509 (June) 1945.

The authors report the results of a study of disturbances of body fluids observed in a 14 month old infant suffering from voluminous watery diarrhea which began at birth.

In contrast with the usual conditions in severe diarrhea, the stools contained chloride in a large excess over sodium, and there was extensive reduction of plasma chloride, with a corresponding increase of bicarbonate. A partial restoration of plasma chloride to its normal level could be sustained by providing an additional intake of sodium chloride, but at the cost of a large increase in the volume of the

stools. There was no appreciable outgo of chloride in the urine. Even when sodium chloride was given by subcutaneous infusion, practically all the chloride was removed in the stools. The diarrhea was evidently the result and not, as is usually the case, the cause of disturbance of water and electrolyte control within the body. The main significance of the observations is the demonstration of the occurrence of an intrinsic defect in government of the body fluids. The nature of this defect was not learned.

AUTHORS' ABSTRACT.

THE SURGICAL TREATMENT OF ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULAS. WILLIAM E. LADD, New England J. Med. **230**:625 (May 25) 1944.

This splendid article does not lend itself well to abstracting and should be read in toto, since it is presented by the pediatric surgeon who has had the widest experience in these cases and the best results. The author presents the following summary.

From the present experience and that of others, it seems fair to conclude that atresia of the esophagus with or without tracheoesophageal fistula should no longer be considered as a hopeless condition carrying with it a 100 per cent mortality. It also seems justifiable to predict that if obstetricians and pediatricians are on the alert for making an early diagnosis the mortality will be further lowered.

It should also be stated that the surgical methods for combating this condition are subject to change. At the present time, however, primary anastomosis of the esophagus appears to be the operation of choice when the two ends of the esophagus can be approximated without too much tension. In other cases, in which the ends of the esophagus are far apart, the three stage operation with the ultimate construction of an anterior thoracic esophagus is a safer procedure. The last 5 patients operated on according to this plan are living and doing well.

GENGENBACH, Denver.

STUDIES OF ENTERIC INFECTIONS IN THE NURSLING AND THEIR TREATMENT WITH SULFONAMIDE COMPOUNDS. ALBERTO MATA LAVIN, Bol. Soc. cubana de pediat. **16**:279 (Aug.) 1944.

A study of 63 cases was made under the usual headings: bacteriology, symptomatology, complications, treatment and others. The author emphasizes the need to study the intestinal flora, especially in infants with "summer" diarrhea, and states that sulfaguanidine is the drug of choice in treating infectious dysentery.

KEITH, Rochester, Minn.

TREATMENT OF INTESTINAL PARASITES WITHOUT LAXATIVES. LORENZO EXPOSITO and ARGELIO DE FERIA, Bol. Soc. cubana de pediat. **16**:489 (Dec.) 1944.

The authors consider useless, and even possibly harmful, the use of "physics" as part of the treatment of intestinal parasitism.

The only modification recommended to the generally accepted treatment is an exclusively carbohydrate diet one day before and during the day of treatment. Four hours after treatment, an enema of althea is used.

KEITH, Rochester, Minn.

THE PATHOGENICITY OF THE PARACOLON BACILLUS. ARTURO CURBELO HERNANDEZ, EMILIO SOTO PRADERA and JOSE R. MONTALVO URRUTIBEASCOA, Bol. Soc. cubana de pediat. **17**:3 (Jan.) 1945.

The authors' study was done during an episode of gastroenteritis in the newborn ward of the "Hospital de Maternidad Obrera de la Habana" that had its highest incidence in August 1943. The total number of patients was 72, and all presented the same clinical picture: (1) diarrhea, without blood, pus or mucus; (2) severe dehydration, and (3) fever, in the more severely ill patients.

Bacteriologic studies of stools of 6 patients were made and all resulted in a pure culture of paracolon bacilli with exactly the same characteristics. A serum

"O" was prepared with one of the species that was able to produce the agglutination of all of them in a dilution of 1 to 600.

Closure of the ward and change to a new one at a distance, sterilization of clothing and linen and protection against flies ended the episode. The authors believe that the fly is an important vehicle for transmission of this type of infection.

KEITH, Rochester, Minn.

## Nervous Diseases

MULTIPLE NEUROPATHY (GRADE 3). JOHN A. TOOMEY and JOHN MESSINA, J. Pediat. **25**:590 (Dec.) 1944.

The term "neuritis" serves as a diagnostic catch bag. Diseases pertaining to the central nervous and the muscular systems are often classed under this head. Names of syndromes and terms describing peripheral neuropathies tend further to confuse rather than to simplify understanding of the terminology. In most books in which neuritis is discussed, attention is directed to disturbances of the ectodermal, or parenchymatous, tissues, as distinguished from involvements of the mesenchymal, or connective, tissues with a dubious distinction, at times, into parenchymatous, perineuritic and interstitial types.

The nervous system responds only in certain ways to a pathologic excitant, regardless of the stimulant. Although there are such conditions as perineuritis, interstitial neuritis and parenchymatous neuritis, distinctions are not too obvious clinically.

In the neuropathies the parenchyma of the nerve rather than the supporting framework is most commonly involved, with few signs of inflammation, merely with degeneration and secondary phagocytosis. However, the end result may be chromatolysis, vacuolation, demyelination, neuronophagia, perivascular infiltration and gliosis.

Clinically, the patient may have sensory, motor and vasomotor signs and symptoms, and from a clinical standpoint the neuropathies could be subdivided into four grades of severity.

In neuropathy grade 1 there would be a single, local neuropathy, the type which follows a cold, exposure, fatigue, pressure, diphtheria, etc., with localized paralysis.

In neuropathy grade 2 there would be severe involvements of many nerves of the extremities or the body, such as follow postdiphtheritic paralysis, lead neuritis and other conditions.

In neuropathy grade 3 there would be all the conditions now termed "toxic neuronitis" (infective neuronitis, toxic neuropathy, infectious polyneuritis, radiculitis, myeloradiculitis, radiculoneuritis, Guillain-Barré syndrome, polyradiculoneuritis acuta [by the French], toxic neuraxonitis, multiple neuritis, motoneuronitis, possibly Landry's disease and others).

Physicians should familiarize themselves with the terms "toxic neuropathy" and "toxic neuronitis" because they have crept into use, but the term "neuropathy grade 3" would give the practitioner a better conception of the underlying pathologic anatomy.

Neuropathy grade 4 would include the conditions of patients who have associated involvements of cord or brain components (acute disseminated encephalomyeloneuronitis, encephalomeningoradiculitis, infective meningomyeloneuritis) but with the neuropathy as the outstanding feature.

Because of the authors' interest in poliomyelitis, many persons have come under their observation whose disease had been diagnosed as infantile paralysis, when, in many instances, they had neuropathy grade 3. TOOMEY, Cleveland.

BLOOD PLASMA IN THE TREATMENT OF ENCEPHALITIS LETHARGICA AND POLIOENCEPHALITIS. PERCIVAL NICHOLSON, J. Pediat. **26**:298 (March) 1945.

The present paper deals with 2 cases, 1 of encephalitis lethargica and 1 of polioencephalitis.

CASE 1.—The patient was a white girl aged 9 years. Three weeks before admission she had a moderate attack of rubella. On May 18, 1943 she was transferred to the Bryn Mawr Hospital isolation ward with a provisional diagnosis of meningitis. The examination showed a very sick child with eyes closed and in a pronounced stupor. When spoken to, she could be aroused, answered questions in a languid manner and complained of severe frontal and occipital headache. Her face showed a noticeable purpuric eruption. She was found to have a stiffness of the neck with pain on motion. All nerve reflexes were exaggerated. The temperature was 101.4 F. After numerous laboratory tests a diagnosis of encephalitis lethargica was made.

It may be assumed that in acute inflammatory involvement of the brain a state of edema exists and that this edema is, at least in part, responsible for pressure against the unyielding cranium, with signs of pressure. If the condition persists it produces degenerative changes through anoxemia. In other words, the physical rather than the direct toxic effect may be responsible for most permanent damage in cases of encephalopathies. To reduce this localized edema, pooled adult blood plasma was resorted to in view of previous results in shock.

On May 21, the patient was given 100 cc. of freshly pooled adult blood plasma. On May 22, she felt better, stiffness of the neck was gone, headache was relieved, photophobia had disappeared and the temperature was lower. Additional freshly pooled adult blood, 120 cc., was given intramuscularly. On May 23, all symptoms were relieved and the patient was convalescing. On June 2, the patient was discharged, clinically well. An electroencephalogram made June 22 revealed some abnormalities chiefly in the frontal and parietal areas in both hemispheres. A second electroencephalogram was made on September 9, which showed that the abnormalities noted on June 22 had disappeared.

As a result of this experience it seemed to the author that for another virus condition, anterior poliomyelitis, for which there is also no specific cure, the same type of treatment would be applicable. It has been suggested that the muscular paralysis from destruction of nerve cells in anterior poliomyelitis is due to intense edema around the motor nerve cells, depriving them of their blood supply and causing their death, and that virus itself plays only a secondary role.

CASE 2.—On October 23, 1943, a white girl (D. W.) aged 8 years was admitted at 6:50 p. m. to the Children's ward, with generalized convulsions, the third attack of the day. Five days before her admission the child had vomited and had diarrhea, which persisted. She had a severe headache the day before admission. During the morning of the day on which she was admitted she became irrational, lethargic and irritable. During the afternoon she had generalized convulsions and was brought to the accident ward. At 7 p. m. she was placed in an oxygen tent. On account of convulsions, from cerebral edema, 500 cc. of pooled adult blood plasma was given intravenously and was all absorbed by 7:45 p. m.

On October 24, 250 cc. of blood plasma was given intravenously.

On October 26, the patient had only slight power in both legs and paralysis was severe. A diagnosis of poliomyelitis was made. She had occasional pains and extreme tenderness in the popliteal muscles. Two hundred and fifty cubic centimeters of pooled adult plasma was given intravenously.

On October 29, the child was given 250 cc. of pooled adult plasma in the same manner, and the Kenny treatment was started.

On November 12, the patient was talkative and had surprising ability to move her arms and legs.

On April 10, 1944, the physician reported, "At this time I do not find any muscle weakness present. D. W. has now resumed her normal daily activities, with daily rests morning and afternoon."

The 2 cases are presented to suggest a new method of treatment. The case of polioencephalitis reviewed here was of a severe encephalitic type and it is felt that it gave the use of blood plasma a severe test. AUTHOR'S ABSTRACT.

TRAUMATIC ULNAR NEURITIS. R. L. RICHARDS, Edinburgh M. J. **52**:14 (Jan.) 1945.

In classifying the clinical groups seen in the age range of 19 to 53 years, the author assigns a place to fracture of the lower end of the humerus sustained in childhood with a fragment of the lateral humeral condyle remaining ununited. There were 7 such instances in 15 cases of tardy ulnar palsy. In most persons with such a fracture there is a permanent distortion of the elbow joint but little disturbance functionally. Operation consists in transposing the ulnar nerve to the front of the elbow. The author discusses results in 26 cases.

NEFF, Kansas City, Mo.

## Diseases of the Genitourinary Tract

TREATMENT OF GONOCOCCIC VULVOVAGINITIS: A STUDY OF 442 CHILDREN. B. C. COMPTON, R. E. BIEREN, E. G. JONES, B. H. INLOES JR., THEODORE KARDASH and J. M. HUNDLEY JR., J. A. M. A. **127**:6 (Jan. 6) 1945.

The authors report that in 318 (72 per cent) of 442 children with vulvovaginitis the disease was of gonococcic origin. They feel that gonococcic vulvovaginitis is a benign disease suitable for treatment in an outpatient department, although the patients should be isolated at home. Diagnosis can usually be made and response to treatment followed by the use of direct smears. Good results were obtained by the use both of sulfonamide drugs (sulfathiazole and sulfadiazine) and of estrogens (natural and synthetic). The authors believe estrogens, used orally or locally, to be the drugs of choice because of the danger of sensitization to sulfonamide compounds. After smears negative for gonococci have been obtained, the patients should be followed at increasingly longer intervals for one year before being pronounced cured.

BAIRD, Wauwatosa, Wis.

## Diseases of the Ductless Glands; Endocrinology

SUPERFICIAL GANGRENE IN ADOLESCENT DIABETES. H. WHITAKER, Brit. M. J. **2**:469 (Oct. 7) 1944.

Three examples of superficial gangrene in young persons with diabetes are reported. The first patient was a boy of 15 with diabetes of three years' duration, who was admitted to the hospital in coma. Despite good nursing attention, a large area of gangrene involving the right buttock suddenly appeared, which later became secondarily infected.

The second patient was a soldier 24 years old, who was admitted to the hospital in coma. An area of dry superficial gangrene developed on the anterior surface of each knee. The shape and symmetry suggested that they were due to pressure of the bedclothes. Healing required six weeks.

The third patient was a 29 year old man, who by mistake injected insulin intradermally instead of subcutaneously; there resulted small round patches of dry superficial gangrene at the sites of injection.

SHAW, Chattanooga, Tenn. [ARCH. DERMAT. & SYPH.]

## Diseases of the Eye

CONCERNING THE RELATIONS OF THE DEVELOPING OPTIC NERVE TO THE RECESSUS OPTICUS AND THE HYPOPHYSIS IN YOUNG FOETUSES: A STUDY OF SEVEN HUMAN FOETUSES 4 MM. TO 40 MM., INCLUSIVE. H. C. HADEN, Am. J. Ophth. **27**:1 (Oct., pt. 2) 1944.

The sixth de Schweinitz Lecture, delivered before the Section on Ophthalmology of the College of Physicians, Philadelphia, appears as a supplement to

the October issue of the *American Journal of Ophthalmology*. It contains a number of illustrations but does not lend itself to abstracting.

W. S. REESE. [ARCH. OPHTH].

ANTERIOR MEGALOPHTHALMOS AND ARACHNODACTYLY. W. V. STEPHENSON, Am. J. Ophth. **28**:315 (March) 1945.

Stephenson reports a case of arachnodactyly with anterior megalophthalmos. Emphasis is given to the genetic aspects of the disease. There are many variations of anterior megalophthalmos, owing to the infinite disturbances in the genes. The term "anterior dysophthalmos" is suggested for the condition.

W. ZENTMAYER. [ARCH. OPHTH.]

A CONTRIBUTION TO THE STUDY OF ANOPHTHALMIA WITH DESCRIPTION OF A CASE. T. ROGALSKI, Brit. J. Ophth. **28**:429 (Sept.) 1944.

The anomaly was seen in a full term male child who died of miliary tuberculosis of "nearly all the organs" at the age of about 10 weeks. The left side of the mouth was enlarged, and there was a V-shaped cleft pointing to the left orbit and connected with it by a slight groove in the skin. Another groove extended from the right angle of the mouth to the right ear; the right two thirds of the upper jaw, i. e., the part to the right of the harelip, projected beyond the mandible, and the nose slanted downward to the right. The right orbit and eyeball appeared normal, but there was no sign of the left eyeball. No malformations were noted in any other region of the body.

Rogalski suggests that in all cases in which the essential parts of the eye, i. e., the retina proper and the lens, are lacking, whether the mesodermal constituents and the pigment epithelium are present or not, the term anophthalmia should be employed. The term microphthalmia should be reserved for cases in which all the ocular constituents, including the retina proper (or the optic nerve) and the lens, are present either underdeveloped or malformed or only vestigial.

Anophthalmia, thus defined, may be classified into two types: 1. Complete anophthalmia, in which no vestiges of the optic outgrowth can be found. In cases of this type it cannot be determined whether the optic vesicle has been formed and suffered complete atrophy or has never been formed at all. 2. Consecutive anophthalmia, in which an optic vesicle or cup has certainly been formed but has atrophied in the very early stages, leaving as its vestige more or less malformed pigment epithelium. Each type may be bilateral or unilateral, and both are almost certainly of genetic origin, the fault being in the neuroblast itself or in other tissues, e. g., in the hematogenic mesoderm, with disturbance of the blood supply.

The author's case belongs to the second type of anophthalmia so defined, and not to the third type described by Ida Mann, as according to her definition it would.

The article is illustrated.

W. ZENTMAYER. [ARCH. OPHTH.]

SULFONAMIDE THERAPY IN OPHTHALMOLOGIC CONDITIONS IN INFANCY. V. RE BENJAMIN, Arch. am. de med. **18**:71 (Oct.-Dec.) 1942.

The importance of ophthalmia neonatorum as a cause of permanent blindness is considered. The incidence in institutions for the blind in Argentina, Uruguay and Brazil has been 35.6, 36.5 and 40.23 per cent. The lack of cooperation in following Credé's procedure, due to ignorance among the population in rural communities, is responsible for the persistent frequency of the disease. In this condition the use of sulfonamide therapy has brightened the outlook considerably. Not only has the duration of the illness been shortened considerably (thirty to eight days), but the care of the patients has been greatly simplified. The importance of early therapy is stressed; once the nutrition of the cornea has

been irreparably affected nothing can be accomplished. The ideal dose is that which maintains a blood concentration of the drug between 6 and 10 mg. per hundred cubic centimeters. As determinations cannot be easily followed in practice, the author has used 0.04 to 0.06 Gm. per kilogram per day. The treatment is maintained for eight days. Four patients with ophthalmia were treated by the author, with splendid results.

ABALLI, Habana, Cuba.

CASUISTIC CONTRIBUTION TO THE MARCUS GUNN SYNDROME. M. ARTIGAS and V. A. VICTORIA, Arch. de oftal. de Buenos Aires **19**:100 (Feb.) 1944.

Two atypical cases of this syndrome are reported. One patient, a girl 17 years of age, had no ptosis of the superior lid, but when the mandible was lowered the left upper lid would rise. The other patient, a boy 10 years of age, with congenital ptosis of the left upper lid, showed elevation of the ptosed lid on swallowing. In his case the synergism was between the third and the ninth nerve. The article is illustrated.

H. F. CARRASQUILLO. [ARCH. OPHTH.]

UNUSUAL PRELACRIMAL CONGENITAL MALFORMATION. M. SORIA ESCUDERO, Arch. Soc. de oftal, hispano-am. **3**:471 (Nov.-Dec.) 1943.

A boy 6 years of age presented a small congenital sinus, about 2 mm. deep, in the region of the lacrimal sac, immediately below the canthal ligament. There was no connection with the sac.

The author has been unable to find in the literature any previous report of such a condition.

H. F. CARRASQUILLO. [ARCH. OPHTH.]

ALOPECIA AREATA (PELADA) OF THE EYELIDS. H. MARBACK, Arq. brasil. de oftal. **6**:211 (Dec.) 1943.

Marback reports the case of an adolescent boy of 14 years who presented total alopecia areata (pelada) of the left upper eyelid. The eyes showed no other abnormality and functioned normally. The age of the patient at the time the condition appeared was not known. There was no history of local trauma or of the use of any local drug. One of the parents had syphilis. The patient was observed for about two months, during which the alopecia was limited to the left upper eyelid. Antisyphilitic therapy, consisting of administration of quinine bismuth iodide, was carried for about three months, in the course of which the eyelashes reappeared and grew normal and permanent, remaining so at the time of the report, two years and a half after discontinuation of the therapy.

W. ZENTMAYER. [ARCH. OPHTH.]

TOTAL ALBINISM OF THE EYES: REPORT OF A CASE. O. CORREA NETTO, Arq. brasil. de oftal. **7**:13 (Feb.) 1944.

Netto reports the case of a man 22 years of age with total depigmentation of the eyeballs. The patient has a brother and a maternal uncle who are albinos. The rest of the family, including several brothers of the patient, are normal. The function of the retina of albinos is not involved. Dark adaptation and perception of colors are normal. Avitaminosis A and B play no role in albinism. The condition is familial, hereditary, recessive and dominant and is favored by consanguinity. Marriage of albino persons should be interdicted for eugenic reasons.

W. ZENTMAYER. [ARCH. OPHTH.]

A CASE OF PERSISTENCE OF THE HYALOID ARTERY: INTERESTING ASPECT OF ITS OPHTHALMOSCOPIC IDENTIFICATION. N. P. DE FIGUEIREDO, Rev. brasil. de oftal. **2**:121 (March) 1944.

De Figueiredo identified the hyaloid artery in the eye of a man 26 years of age. The patient exhibited dental abnormalities of intrauterine origin. The author believes that the persistence of the hyaloid artery depends on a sudden

cessation of the involution of the artery during the last few months of intrauterine life due to syphilis, which increases in virulence during the last few months of pregnancy. Syphilis is also the cause of the dental abnormalities which are often associated with persistence of the hyaloid artery.

W. ZENTMAYER. [ARCH. OPHTH.]

## Miscellaneous

THE ENHANCEMENT OF THE PHYSIOLOGICAL ECONOMY OF PENICILLIN IN DOGS BY THE SIMULTANEOUS ADMINISTRATION OF PARA-AMINOHIPPURIC ACID II. KARL H. BEYER, LAWRENCE PETERS, ROLAND WOODWARD and W. F. VERWEY, J. Pharmacol. & Exper. Therap. **82**:310 (Dec.) 1944.

Experiments were made when the supply of penicillin was not abundant to learn whether a given quantity of penicillin could be made more efficient by decreasing its rate of excretion by the use of sodium paraaminohippurate. In dogs, it was found that continuous infusion of this drug did produce this effect on single intravenous injections of penicillin, from the following experimental results:

1. The prolonged maintenance of a determinable plasma concentration of penicillin.

2. A noticeable prolongation of the period of time over which penicillin was excreted.

3. A definite decrease in the rate of excretion of penicillin.

4. A pronounced decrease in the amount of penicillin recovered from the urine in a given period.

Clinical studies are also in the process of investigation.

PILCHER, Cleveland.

ANTAGONISTS FOR THE CIRCULATORY DEPRESSION OF QUININE INJECTED INTRAVENOUSLY AND THE IMPLIED CHOLINERGIC ACTION, AND NATURE AND IMPORTANCE OF THE VASODILATATION, IN THE DEPRESSION. ROBERT H. DREISBACH and P. J. HANZLIK, J. Pharmacol. & Exper. Therap. **83**:167 (March) 1945.

In spite of its undesirable circulatory action, it has been found necessary to use quinine by vein in the most serious states of malaria, viz., the cerebral form and coma. Studies were made on cats and rabbits, the details of which need not be given. It was found that three of the thirty-two agents tested when mixed with the quinine in doses of 10 mg. per kilogram were capable of preventing or mitigating the depression, namely, epinephrine (0.015 to 0.02 mg. per kilogram) as the most efficient and desirable, neo-synephrine, (0.05 mg. per kilogram) about equal to epinephrine and next in order and calcium chloride (10 mg. per kilogram) the least efficient and desirable.

Transferred to a 70 Kg. man and the same actions assumed, the total doses of the most desirable agents for use in severe quinine collapse would be: epinephrine, 1.4 mg. or neo-synephrine, 3.5 mg., well diluted and injected intravenously and cautiously.

References are given concerning the clinical use of quinine in malaria.

PILCHER, Cleveland.

HYDRATION BY CONTINUOUS DRIP WITH RHINOESOPHAGIC CATHETER. PROSPERO AMIAGORA SEGUEL, Pediat. Américas **2**:186 (March) 1944.

The article describes the use of a French catheter no. 6-8 introduced through the nose and reaching the middle part of the esophagus for use in maintaining a continuous drip for dehydrated patients. Isotonic solution of sodium chloride given by this procedure and sulfathiazole controlled the vomiting. The catheter can be left five or six days, but it should be changed from one side of the nose to the other every forty-eight hours. Hydration was obtained, and tolerance to the procedure was good.

DE LA TORRE, Rochester, Minn.

# News and Comment

## SCHOOL PSYCHIATRIST

**Bureau of Child Guidance, Board of Education, City of New York**

*Salary $6,000 to $7,000 per Annum*

The Board of Examiners announces examinations for the license of School Psychiatrist, to be given in March 1946. The position carries the advantages of liberal retirement and pension and civil service tenure. The salary starts at $6,000 and is raised to $7,000 in three years.

The general requirements are:

Age 30 to 45 years; graduation from a grade A medical college, and either (*a*) five years of practice in psychiatry, including 800 hours in an approved institution for mental diseases and 1,200 hours in an approved child guidance clinic or (*b*) three years of practice in psychiatry, including 1,200 hours in an approved mental institution and 1,200 hours in an approved child guidance clinic.

Further information about these requirements and the examinations will be obtained with the application. The final date for filing applications is Feb. 25, 1946. Application forms may be obtained in person or by writing to: Board of Examiners, Room 437, Board of Education, 110 Livingston Street, Brooklyn 2, N. Y. The written request must be accompanied with a large, self-addressed envelope bearing 6 cents in stamps.

## GENERAL NEWS

**The American Board of Pediatrics, Inc., Elects Officers.**—At the annual meeting of the American Board of Pediatrics, Inc., in Atlantic City, N. J., Dec. 6, 1945, the following officers were elected:

Dr. C. Anderson Aldrich, president, Rochester, Minn.

Dr. Donovan J. McCune, vice president, New York.

Dr. Lee Forrest Hill, secretary-treasurer, Des Moines, Iowa.

(All communications to the secretary should be addressed to the American Board of Pediatrics, Inc., 3309 Forest Avenue, Des Moines, Iowa.)

Dr. Charles F. McKhann, Cleveland, was elected a new member of this Board by the Section on Pediatrics of the American Medical Association, for a term of six years, to replace Dr. Franklin P. Gengenbach, who retired.

**The American Board of Pediatrics, Inc.**—The American Board of Pediatrics, Inc., will hold a written examination on March 22, 1946, locally, under a monitor. Oral examinations will be held in Cleveland on April 27 and 28, 1946 and at San Francisco at the time of the Ninety-Fifth Annual Session of the American Medical Association (July 1 to 5), if sufficient applications are received to warrant this examination.

**Application Fee for the American Board of Pediatrics, Inc.**—On and after May 1, 1946, the application fee for the American Board of Pediatrics, Inc., will be $100.

**American Academy of Pediatrics.**—There will be a meeting of Region III of the American Academy of Pediatrics on May 6, 7 and 8, 1946, at the Netherlands Plaza Hotel, Cincinnati.

## NOTICE

**Preceptorships.**—It has come to the attention of the American Board of Pediatrics, Inc., from several sources that an erroneous impression is being passed around regarding preceptorships. Preceptorships will not be acceptable as preliminary pediatric training but may be used as refresher work and as accredited time in practice by those who have completed their preliminary training.

# Book Reviews

**Spina Bifida and Cranium Bifidum.** By Franc D. Ingraham, M.D. Price, $2. Pp. 85, plus bibliography, with 28 figures and 8 tables. Cambridge, Mass.: Harvard University Press, 1944.

The publication in book form of these five papers on spina bifida and cranium bifidum, originally appearing in the *New England Journal of Medicine,* deserves an enthusiastic reception by those interested in pediatrics. The papers present a clear picture of the problems involved in diagnosis and treatment and show that in many cases of these defects the prognosis is better than is usually conceded.

The chapter on occult spinal disorders shows the relationship of maldevelopment of the feet or lower extremities and disturbances in gait to an underlying spinal abnormality. Thirty-one of 65 patients whose cases were studied were first seen in the orthopedic clinic.

The chapter on the Arnold-Chiari malformation, showing the association of this condition, in which there is a downward elongation of the cerebellum and brain stem into the cervical position of the bony spinal canal, with meningocele and myelomeningocele, is of unusual interest. The cases reported were studied at the Boston Children's Hospital, where Dr. Ingraham is the neurosurgeon.

A comprehensive bibliography includes in the neighborhood of two thousand references. References to material published previous to 1850 are grouped together, and the subsequent ones are grouped in ten year periods.

**Carbon Monoxide: Its Hazards and the Mechanism of Its Action.** By W. F. von Oettingen. Federal Security Agency, United States Public Health Service, Public Health Bulletin No. 290. From the Industrial Hygiene Research Laboratory, National Institute of Health. Price, 35 cents. Pp. 257, with 26 illustrations and 30 tables. Washington, D. C.: United States Government Printing Office, 1944.

While this book from the Industrial Hygiene Research Laboratory of the National Institute of Health is concerned chiefly with industrial poisoning and says practically nothing about children, it should not be overlooked by any one who wishes to make a thorough study of carbon monoxide poisoning.

The chemistry is thoroughly covered. The sources of carbon monoxide poisoning given are mostly those in industry. Those that might concern children are the various gas-fired heaters, furnaces and coal stoves. Automobile exhausts, gas leaks and charcoal heaters also contribute to the fatalities. Although the toxic properties of illuminating gas are mainly due to its content of carbon monoxide, it is more acutely toxic than this content would indicate.

Studies have been made of the concentration of carbon monoxide in city streets. Even in crowded traffic and even with continued exposure the concentrations are below the dangerous levels. Studies made on 156 traffic officers stationed in the Holland tunnel are cited. Chronic poisoning does not occur, but subacute poisoning is not uncommon. The vague symptoms sometimes reported in compensation cases may have a psychic factor.

In the final analysis, the toxic effect of carbon monoxide is suffocation, and Haldane is quoted, "Anoxemia not only stops the machine, but wrecks the machinery."

Regarding treatment, the most important measures are the administration of oxygen and the supplying of artificial respiration. Chilling and physical exercise should be avoided. In order to prevent hyperemia and edema of the brain, venesection, spinal puncture and intravenous injection of hypertonic solutions have been used.

An excellent bibliography is given.

**Diseases of the Nervous System in Infancy, Childhood and Adolescence.** Second edition. By Frank R. Ford, M.D. Price, $12.50. Pp. 1,143, with 164 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

In 1937 Ford wrote a comprehensive volume with the same title, and this is the second edition.. While the first edition was complete, this volume contains reports on many conditions and many discussions not included in the first volume.

Among the inclusions in this volume are a discussion of the Arnold-Chiari malformation, electroencephalography for the diagnosis of epilepsy, involvement of the nervous system in anemia, the latest treatment of hyperthyroidism, disorders of lipid metabolism, hemorrhagic disease of the newborn, sulfonamide compounds in the treatment of brain abscess, the age of onset of myasthenia gravis and many others.

The titles of the twelve chapters of the book are: Examination of the Nervous System; Clinical Aspects of the Anatomy and Physiology of the Nervous System; Prenatal Diseases of the Nervous System; Heredofamilial and Degenerative Diseases of the Nervous System; Infections and Parasitic Invasions of the Nervous System; Toxic and Metabolic Disorders Involving the Nervous System; Vascular Lesions and Circulatory Disorders of the Nervous System; Neoplasms and Reflected Conditions Involving the Nervous System; Injuries of the Nervous System by Physical Agents; Diseases of the Autonomic System, and Diseases of the Muscles and Syndrome and Syndrome Groups.

This volume is authoritative and well written. It is an excellent detached text and an indispensable reference book.

**The New-Born Infant: A Manual of Obstetrical Pediatrics.** Third Edition. By Emerson L. Stone, M.D. Price, $3.25. Pp. 314. Philadelphia: Lea & Febiger, 1945.

The material in this book is the outgrowth of an elective course of lectures given to senior medical students. The aim is to correlate and arrange a mass of data that is otherwise scattered throughout the literature. The author is associate professor of gynecology and obstetrics at Yale University School of Medicine. He fully recognizes the responsibility of the obstetrician for the neonatal condition of the child, discussing the relative values and dangers of various obstetric procedures and of the use of anesthetics and sedatives. He also urges the obstetrician to cooperate in efforts to establish breast feeding.

The chapters on the immediate care of the newborn and on the physiology and development of the newborn are unusually well written, and, although some controversial material is presented, it is not confusing. The technic of breast feeding, the pathologic aspects of lactation and the methods of artificial feeding are fully considered. The chapter on the dietary disorders of infancy is less detailed. In chapters on birth injuries and infections and disorders of special systems, the author discusses treatment as well as pathology and diagnosis. The concluding chapter is on the care and prognosis of the premature infant.

A full index is provided.

**The Control of Communicable Diseases: An Official Report.** By the Subcommittee on Communicable Disease Control of the Committee on Research and Standards, American Public Health Association. Sixth edition. Paper. Price, 35 cents. New York: American Public Health Association, 1945.

This booklet should be a companion to the "Report of the Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals of the American Academy of Pediatrics." There is much that never may be needed, but that which is useful is well put, succinct and authoritative. It deals with agents, methods of diagnosis, methods of transmission, methods of control of disease and other topics. The report of the American Academy of Pediatrics is mainly on therapy, and hence this volume could be considered supplementary and of value to all practitioners.

# Directory of Pediatric Societies *

## INTERNATIONAL

### International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.

Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

### International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.

Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.

Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.

Place: New York. Time: Postponed indefinitely.

### International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

## FOREIGN

### Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.

General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

### Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Vicente Lara.

First Secretary: Dr. Armando de Arruda Sampaio.

Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.

Time: Twelfth of every month, 8:30 p. m.

### British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham.

Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

### Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.

Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

### Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.

Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage.

Place: Different places. Time: Three times a year.

### Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.

Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Prof. Norman Capon, 49A Rodney St., Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Teodosio Valledor Campo, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado, 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

SOCIEDAD ECUADORIANA DE PEDIATRIA

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

SOCIEDAD DE PEDIATRIA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texidó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pedro J. Alvarez.
Secretary: Dr. Ernesto R. Figueroa, 3a Avenida 10, Bella Vista, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. José Alberto Praderi, Eduardo Acevedo 1132, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo.

## NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.
Place: San Francisco. Time: July 1-5, 1946.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Time: Jan. 15-18, 1946.
Region I. Place: Hotel Pennsylvania, New York. Time: April 2-4, 1946.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. C. Anderson Aldrich, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis 8.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. H. S. Little, 300 Dufferin Ave., London, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, 67 College St., Toronto 2.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Edward M. Bridge, 219 Bryant St., Buffalo, N. Y.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia 46.

## SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Robert Alway, University of Utah School of Medicine, Salt Lake City 2.
Secretary-Treasurer: Dr. L. Paul Rasmussen, 1020 Boston Bldg., Salt Lake City 1.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. William P. Buffum, 122 Waterman St., Providence, R. I.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Percy Guy, 502–2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.
Place: Banff, Canada. Time: June 11, 1946.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. George B. Logan, 102 Second Ave. S. W., Rochester, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary: Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

## STATE

### Alabama Pediatric Society

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.

### Arizona Pediatric Society

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

### Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

### California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.

### Florida State Pediatric Society

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

### Georgia Pediatric Society

President: Dr. Ruskin King, 10 W. Taylor St., Savannah.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

### Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Time: Three meetings a year.

### Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

### Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

### Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

### Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.
Place: Same as State Society. Time: Same as State Society.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.
Place: Detroit. Time: September 1945.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. John L. Gedgoud, University of Nebraska Hospital, Omaha.
Secretary-Treasurer: Dr. Gerald C. O'Neil, 640 City National Bank Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Arthur H. London Jr., 1105 W. Main St., Durham.
Secretary: Dr. Jay M. Arena, Duke Hospital, Durham.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. John Mott Rector, 2000 Van Ness Ave., San Francisco.
Secretary: Dr. George Bates, 490 Post St., San Francisco 2.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. G. R. Russell, 604 S. Cincinnati Ave., Tulsa.
Secretary: Dr. Luverne Hays, 108 W. 6th St., Tulsa.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Lonita Boggs, 301 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, 429 Wade Hampton Office Bldg., Columbia 10.

TEXAS PEDIATRIC SOCIETY

President: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. L. E. Sutton Jr., Medical College Hospital, Richmond.
Secretary: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.

## LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. Charles L. Ruggles, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Walter Heymann, 2103 Adelbert Rd., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. John M. Ross, 530 St. Claire Ave. W., Toronto, Canada.
Secretary: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Place: Academy of Medicine. Time: Third Thursday of each month.

BRONX PEDIATRIC SOCIETY

President: Dr. Jacob H. Turner, 121 W. 197th St., New York.
Secretary: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Second Wednesday of each month; except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Kenneth G. Jennings, 159 Midwood St., Brooklyn.
Secretary: Dr. Joseph Battaglia, 713 Bushwick Ave., Brooklyn 21.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of each month except May, June, July, August and September.

BUFFALO PEDIATRIC SOCIETY

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Louis W. Sauer, 636 Church St., Evanston, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Children's Memorial Hospital, 707 Fullerton Ave. Time: Third Tuesday of each month.

CINCINNATI PEDIATRIC SOCIETY

President: Dr. Theodore K. Selkirk, 3605 Edwards Rd., Cincinnati.
Secretary: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

### Dallas Pediatric Society

President: Dr. Robert A. Knox, 3701 Fairmount Ave., Dallas 4, Texas.
Secretary-Treasurer: Dr. Gladys J. Fashena, 4585 Belfort Pl., Dallas 4, Texas.
Place: Children's Medical Center. Time: 1 p. m., second and fourth Saturdays of each month.

### Detroit Pediatric Society

President: Dr. Philip J. Howard, 2977 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. John C. Montgomery, 564 Fisher Bldg., Detroit 2, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., second Wednesday of each month, four meetings a year.

### Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

### Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

### Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

### Los Angeles County Medical Association, Pediatric Section

President: Dr. Milo B. Brooks, 1033 Gayley Ave. W., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

### Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Abraham M. Litvak, 1145 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m. fourth Monday of each month, October to April, inclusive.

### Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02–91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

### Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

### Memphis Pediatric Society

President: Dr. W. L. Rucks, 1074 Madison Ave., Memphis, Tenn.

Secretary-Treasurer: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.

### Milwaukee Pediatric Society

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.

Secretary-Treasurer: Dr. B. J. Malnekoff, 3213 N. Marietta Ave., Milwaukee 11.

Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

### New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred E. Fischer, 73 E. 90th St., New York.

Secretary: Dr. Robert O. Du Bois, 122 E. 76th St., New York.

Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

### Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 625½ N. W. 10th St., Oklahoma City.

Secretary: Dr. Jeanne Shotstall, 625½ N. W. 10th St., Oklahoma City.

Place: Oklahoma Club. Time: Third Thursday of each month.

### Philadelphia Pediatric Society

President: Dr. Ruth Hartley Weaver, 1719 Rittenhouse St., Philadelphia.

Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia 46.

Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday in October, December, February and May.

### Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.

Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.

Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

### Puget Sound Pediatric Society

President: Dr. D. M. Dayton, 740 St. Helens Ave., Tacoma.

Secretary: Dr. W. B. Chesley, 1306 Madison St., Seattle 4.

Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

### Richmond Pediatric Society

President: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.

Secretary-Treasurer: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.

Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

### Rochester Pediatric Society

President: Dr. William L. Bradford, 260 Crittenden Blvd., Rochester 7, N. Y.

Secretary-Treasurer: Dr. Donald D. Posson, 222 Chili Ave., Rochester 11, N. Y.

Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

### St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.

Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis.

Place: Branscome Hotel. Time: 7:00 p. m., third Thursday of each month from November to June.

### Southwestern Pediatric Society

President: Dr. William Belford, 420 Walnut St., San Diego, Calif.

Secretary: Dr. Robert J. Dostal, 710 Wilshire Blvd., Santa Monica, Calif.

Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

### University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.

Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

### Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.

Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.

Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.